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TREATMENT OF INTUSSUSCEPTION CAUSED BY INVAGINATED MECKEL'S DIVERTICULUM

Report of a Case, with a Review of Experience in a Community Hospital

RAYMOND W. GADBOIS, M.D.,* MICHAEL A. DEAN, M.D.,† AND WILLIAM E. JOHNSON, M.D.‡

WORCESTER, MASSACHUSETTS

SINCE we believe that the experience of a small community hospital is of importance in evaluating surgical statistics, it is hoped that the following report will be of interest, particularly in comparison with reports from larger, more specialized hospitals.

Meckel's diverticulum, first recorded by Lavator, described in 1700 by Littre, labeled a diverticulum by Ruysh and Mery, was further reported by Morgagni, and finally recognized as a cause of abdominal complaints by John Frederick Meckel.[1]

Embryologically, Meckel's diverticulum results from a failure of the intestine to lose its connection with the yolk sac. Developmentally, failure to lose this connection may lead to the diverticulum or persistent omphalomesenteric duct, or any combination of conditions between the two. Statistically, it occurs in approximately 2 per cent of the general population and somewhat more commonly in the male.

Meckel's diverticulum is of importance because it may become inflamed, hemorrhage, adhere to mesentery or bowel, form a nidus of internal hernias, form the focal point of a volvulus or act as a foreign body causing intussusception. For clarity the complications may be divided into primary, including acute inflammation, peptic ulcer, fecal fistula, tumor formation and chronic inflammation, and secondary, comprising intestinal obstruction due to acute inflammatory adhesions, bands and internal hernias, volvulus or intussusception.

Acute inflammatory changes in Meckel's diverticulum may closely simulate the signs, symptoms[2, 3] and course of acute appendicitis. The natural history of the individual case may vary somewhat depending on the patency and diameter of the stoma, but it may undergo secondary gangrene and necrosis and result in peritonitis by rupture, much in the same manner as an acute appendicitis. Likewise, acute Meckel's diverticulitis has similar serious complications, such as local abscesses with inflammatory adhesions and possible intestinal obstruction.

Heterotopic tissue[4] in the diverticulum occurs more commonly in association with ileal mucosa than ileal mucosa appears alone. Peptic ulceration in close proximity to heterotopic gastric tissue is a well known complication. More often it manifests itself as gross painless melena, but occasionally it erodes through the serosa and gross hemorrhage into the peritoneal cavity results.

The patent persistent omphalomesenteric duct is often diagnosed by the occurrence of a mucoid discharge from the umbilicus. When the duct is widely patent throughout its length,[5] it serves as a fecal fistula and, if active, can lead the patient into the physiochemical imbalances of an overactive ileostomy.

Tumors as well as tuberculosis can occur in Meckel's diverticulum.

The most important secondary complication of Meckel's diverticulum is intestinal obstruction, manifested in one of the four following ways:

Acute inflammatory adhesions can give rise to an early acute mechanical obstruction. As in any other acute intra-abdominal process, the natural process of containment plasters mesentery, loops of bowel and omentum over and near the site of inflammation. An acute inflammatory mechanical obstruction can be a natural sequela of this process.

Meckel's diverticulum can directly or indirectly cause internal hernias, either as a persistent band from bowel to umbilicus[3] or by attachment of the free tip to any portion of the visceral or parietal peritoneum, thus forming bands through which bowel might prolapse and be unable to reduce itself. The herniated bowel may vary from a small portion of a loop to a whole segment of bowel, most often, of course, the small bowel. If untreated, the condition may quickly pass through all the stages of irreducible exter-

*Visiting surgeon, St. Vincent Hospital.
†Resident in surgery, St. Vincent Hospital.
‡Assistant resident in surgery, St. Vincent Hospital.

nal hernia, except that operative interference is apt to be longer delayed because of the difficulty in establishing the diagnosis.

Acting as the hub on a wheel, the diverticulum may cause volvulus of the small intestine.

TABLE 1. *Cases of Meckel's Diverticulum Seen at St. Vincent Hospital from 1930 to December 1, 1948.*

CASE NO.	AGE	SEX	DESCRIPTIVE NOTE	OPERATION	OUTCOME
	yr.				
1	6	M	Invaginated Meckel's diverticulum with intussusception	Reduction of intussusception; excision of diverticulum	Recovery
2	5	M	Acute inflammation with ? perforation	Excision	Recovery
3	39	F	Acute inflammation with ? perforation; intestinal obstruction with adherent loops of bowel.	Excision	Recovery
4	18	F	Large patent diverticulum; internal hernia through band.	Excision	Recovery
5	22	M	Diverticulum (incidental finding)	Excision	Recovery
6	6½	F	Fibrosed band with internal hernia	Excision	Recovery
7	26	M	Acute gangrenous Meckel's diverticulitis with adherent loops of bowel	Excision; lysis of adhesions.	Recovery
8	18	M	Diverticulum (incidental finding) (in patient's own mesentery)	Excision	Recovery
9	4½	M	Persistent omphalomesenteric duct	Excision	Recovery
10	11	F	Diverticulum (incidental finding)	None	Recovery
11	21	F	Diverticulum (incidental finding)	None	Recovery
12	74	M	Diverticulum (incidental finding)	Inversion; choledochogastrostomy for carcinoma of cystic duct.	Death from pulmonary edema after operation
13	17	M	Diverticulum (incidental finding)	Excision	Recovery
14	53	F	Diverticulum (incidental finding)	Excision	Recovery
15	8	M	Irreducible intussusception	Resection, with end-to-end anastomosis	Recovery
16	31	F	Fibrosed band	Excision	Recovery

By far the most interesting complication is intussusception. Progressive and retrograde intussusception have been reported. Several years ago a comprehensive review recorded only 25 clearly defined cases of obstructing intussusception due to invaginated Meckel's diverticulum. More recently, 29 such cases were listed in a series of 610 intussusceptions.[6] Pathologically, invaginated Meckel's diverticulum occurs as a polypoid mass that can cause partial obstruction, intermittent self-reducing intussusception or progressive intussusception requiring reduction or resection in the individual case. The type of intussusception may be ileocolic, ileoileocolic or ileoileal in order of decreasing frequency. When reduction is impossible and more radical measures are required, the attending mortality is of serious proportions.

The results of operation in cases of Meckel's diverticulum and intussusception at St. Vincent Hospital are shown in Table 1 and 2.

TABLE 2. *Cases of Intussusception Seen at St. Vincent Hospital from 1930 to December 1, 1948.*

CASE NO.	AGE	SEX	TYPE OF INTUSSUSCEPTION	CAUSE	OPERATION	OUTCOME
1	4 mo.	F	Ileocolic	Unknown	Reduction	Recovery
2	7 mo.	M	Ileocolic	Unknown	Reduction (performed with difficulty)	Death 8 hr. after operation
3	7 mo.	M	Ileocolic	Unknown	Reduction (performed with difficulty)	Death 4 days after operation
4	10 mo.	F	Ileocolic	Unknown	Reduction	Recovery
5	3 yr.	F	Colocolic	Unknown	Reduction manually and with enema	Recovery
6	57 yr.	M	Ileoileal	Unknown; multiple perforations, irreducible.	Resection with ileoileal anastomosis and preliminary ileostomy	Death 4 days after operation
7	11 mo.	M	Ileocolic	Unknown	Reduction by enema	Recovery
8	79 yr.	F	Ileocolic	Adenocarcinoma of cecum	Primary resection; ileotransverse colostomy.	Recovery
9	54 yr.	F	Ileocolic	Carcinoid of ileum	Resection and primary anastomosis	Recovery
10	42 yr.	F	Ileocolic	Carcinoma of cecum	Reduction; ileotransverse colostomy.	Recovery
11	8 mo.	M	Ileocolic	Unknown	Reduction	Recovery
12	4½ mo.	M	Ileocolic	Unknown	Reduction	Recovery
13	46 yr.	F	Retrograde ileoileal	Carcinoid of ileum	Resection of ileum	Recovery
14	48 yr.	F	Colocolic	Adenocarcinoma of cecum	Resection of cecum and ascending colon	Recovery
15	6 yr.	M	Ileocolic	Invaginated Meckel's diverticulum	Reduction; resection of Meckel's diverticulum.	Recovery
16	8 yr.	M	Ileoileal	Invaginated Meckel's diverticulum	Resection; end-to-end anastomosis.	Recovery

INTUSSUSCEPTION

Intussusception indicates the passage of one segment of bowel into another. It occurs at all ages, varying in frequency and cause at each age period.

For our purpose, cases can roughly be divided into three groups occurring in infancy, childhood and adult life. Intussusception is relatively common in the first few years of life, and the greatest proportion of cases occur in the first two years of life. Etiologically, no satisfactory explanation for the vast majority of cases can be found. Estimates vary, but it is fair to state that approximately 90 to 95 per cent[6] of intussusceptions in infancy are found to have no mechanical cause. A few are due to Meckel's diverticulum, intestinal polyp, lymphomas and ileal duplications. In older children the greater number of intussusceptions, and in adults almost all, have mechanical causes.

Intussusception is a mechanical obstruction, and its complications are first partial or complete obstruction with the attending pathologic sequelae. Some intussusceptions produce a maximum of symptoms, progress a short distance and are reducible. Some offer a minimum of symptoms, progressing rapidly. Cases are reported with spontaneous expulsion of the intussusception rectally. Between these extremes occur the cases that become incarcerated. Owing to compression of blood vessels venous obstruction, extravasation, anoxemia and infarction of bowel occur. Intra-abdominal rupture, with resultant peritonitis, may follow. Toxemia occurs fairly soon, and, if the condition is neglected and allowed to progress, death usually ensues. An analogy can be drawn between an untreated intussusception and an untreated strangulated hernia. The complications and results are similar.

Treatment is, of course, recognition and reduction. Lately, there is a renewed interest in nonoperative reduction, but the vast majority of surgeons prefer operative intervention so that total pathologic damage can be fully evaluated and the necessary corrective measures immediately applied.

Case Report

An 8-year-old boy was admitted to St. Vincent Hospital on October 5, 1948, with a chief complaint of vomiting. He had been well until 4 days prior to admission, when, after eating breakfast, he complained of "pains in the stomach." This did not keep him away from school, but he returned home soon and vomited food residue. During the period before admission he had anorexia and vomited 2 or 3 times a day with short bouts of intermittent abdominal pain. During the 4 days his bowels had been regular, except for 4 loose bowel movements with no pain and no blood. On the day prior to admission he vomited twice, once in the morning and again at 11 p.m. The abdominal pain had become no worse. He denied chills, fever, cough and muscle aches. At no time did he have any rash, hematuria or dysuria. On admission the patient appeared listless. The skin was dry, warm and pallid. He had no adenopathy. The lungs were clear, and the only positive physical finding was deep tenderness in the left hypochondrium. There was no palpable mass, no spasm and no costovertebral-angle tenderness. Peristalsis was low pitched and sluggish.

The temperature was 99.4°F., the pulse 98, and the respirations 20.

Examination of the blood disclosed a red-cell count of 5,180,000, with a hemoglobin of 100 per cent, and a white-cell count of 13,500, with 78 per cent neutrophils.

The patient was admitted to the pediatric service with a diagnosis of gastroenteritis. Fluids were forced by mouth, and overnight he gradually became somewhat distended and had repeated cramping abdominal pain, most severe in the umbilical region and left upper quadrant. At the time of surgical consultation 18 hours after admission the temperature was 99.4°F., the pulse 104, and the respirations 20. He had not been nauseated and had not vomited during the interval since admission. On physical examination he was alert and co-operative and in moderate discomfort. The abdomen appeared slightly distended and was tympanitic throughout. Tenderness was present throughout the abdomen and maximal in the left upper quadrant. Both rectus muscles were spastic, and the spasm increased with paroxysms of pain. Peristalsis was sluggish and barely audible during intervals between pain and moderately high-pitched and tinkling during the pain. Rectal examination was negative, and no abdominal masses were palpated. A

Figure 1. *Plain Film of the Abdomen.*
The localization of the distention to the small bowel suggests mechanical obstruction although it is possible for an adynamic ileus to produce this picture.

plain film of the abdomen revealed marked gaseous distention of the small bowel, with one loop extending well into the pelvis (Fig. 1). An x-ray diagnosis of mechanical obstruction was made.

The surgical service suggested decompression and parenteral administration of fluids, believing that the patient had secondary obstruction on a basis of acute appendicitis, or Meckel's diverticulitis.

After treatment according to the method of Ochsner the patient appeared fairly well and was free of pain, but passed no flatus or feces. Peristalsis disappeared. He received penicillin, streptomycin and parenteral injection of fluids. A Cantor tube was passed, and his progress followed by x-ray films. On the morning of the 5th hospital day a firm mass was found in the right lower quadrant and demonstrated by x-ray examination (Fig. 2).

The mass was regarded as representing a localized appendiceal abscess. Throughout the 6th hospital day the pa-

tient experienced cramping abdominal pain. The mass moved to the epigastrium and then later was found in the left hypochondrium. The abdomen was soft and nontender, with no tenderness over the mass. The pulse had risen to 132, and a diagnosis of progressive intussusception was made. Barium enema revealed a normal colon and distal ileum. The previously noted mass in the right lower quadrant was absent on x-ray study (Fig. 3).

The patient was returned to the ward for continued observation. During the night he required Demerol for pain. In the morning he was observed during an attack of pain in which he doubled his legs up on his abdomen. However, the abdomen was soft and nontender with the mass again in the right lower quadrant. Operative interference was elected. The preoperative diagnoses were internal hernia, volvulus and omental cyst with ? volvulus.

Dilated loops of small bowel extruded through the abdominal incision. The aforementioned mass was easily

FIGURE 2. *Roentgenogram Taken with the Tip of the Cantor Tube in the Duodenum.*

A fairly definite soft-tissue mass is outlined in the right lower quadrant. The small-bowel distention appears less at this time.

found, mobilized out of the right lower quadrant, and proved to be an ileoileal intussusception, the intussusceptum measuring approximately 46 cm. With gentle milking behind the head of the intussusceptum a reduction back to approximately 14 cm. from its origin was possible. When greater pressure was exerted, a transverse tear occurred in the serosa. Taxis on the intussusceptum was ineffectual, and immediate resection was considered necessary. The abdominal cavity was packed off. The loop of bowel was brought out on the abdomen and the entire procedure performed extra-abdominally. Viable bowel was selected proximally and distally and divided between clamps with cautery. A primary end-to-end anastomosis with three layers of sutures was performed. The bowel had been sectioned at an angle of about 70° to ensure an adequate stoma, and the little finger could easily pass through the stoma. The site of the anastomosis was determined to be approximately 75 cm. from the ileocecal valve.

When the specimen was opened, the head of the intussusceptum was found to be an invaginated Meckel's diverticulum (Fig. 4).

FIGURE 3. *Roentgenogram of the Abdomen in Which the Soft-Tissue Mass Previously Observed in the Right Lower Quadrant Is No Longer Apparent.*

The small bowel remains distended, but slightly less so than on the initial examination. After a barium enema the colon filled easily and normally, and the barium also passed freely into the terminal ileum. The appendix filled in the normal position. No pressure defects could be demonstrated on the bowel, and there was no evidence of disease in the colon.

Postoperatively the patient's convalescence was complicated by peritonitis, which quickly subsided, and he was

FIGURE 4. *Opened Specimen, Showing How the Meckel Diverticulum Invaginated and Acted as the Head of the Intussusceptum.*

discharged well on the 13th postoperative day with the wound healed by first intention.

Discussion

One of the factors causing a high mortality in patients with irreducible intussusception is the time lost in either hospitalizing the patient or establishing the diagnosis. Lately, in our attempts to arrive at a specific diagnosis and in the extensive use of diagnostic aids (x-ray study and so forth), we may on occasion be guilty of what we are sure is just criticism by our older confreres — namely, unwarranted delay in operative exploration.

In this particular case the patient's symptoms were interpreted as being caused by a perforated appendix with peritonitis. He was treated according to the method of Ochsner. When a mass in the right lower quadrant developed, the diagnosis seemed fully established until the mass was noted to move. His abdomen did not distend because of Cantor-tube drainage. There were no physiochemical imbalances, because of adequate parenteral replacement. Toxemia was minimized by intubation, parenteral administration of fluids and antibiotics. When the abdominal mass moved, intussusception was considered, and a barium enema given to establish the diagnosis. Normal barium enema ruled out an enterocolic intussusception. After barium enema, symptoms increased in severity, cramping abdominal pain developed, the patient grew more restless, and the pulse accelerated. In view of the patient's clinical condition operation was considered necessary. At no time had he passed flatus or feces, and no blood was found on rectal examination to aid in the diagnosis. Although the therapeutic triad of suction, fluids and antibiotics without doubt masked the true abdominal picture, their use probably improved the preoperative condition of the patient.

Intestinal obstruction in a child beyond two years of age can be caused by Meckel's diverticulum and should be considered[7] in differential diagnosis. A history of severe intermittent abdominal pain, vomiting and melena followed by small amounts of bright-red blood is the most reliable diagnostic aid.[8] Usually, a palpable abdominal mass can be found, although initially it may be small enough to escape detection. With or without the mass the diagnosis should be considered. Lately x-ray proof of intussusception is not being routinely employed[6, 9] because of time lost during the procedure and the fact that a small percentage of cases will not be diagnosed. If the intussusception is an ileoileal one it may be missed, as was true in the case reported above.

Most surgeons believe that the less done, the better in the original reduction. Unless more radical measures are distinctly indicated, they should be deferred to a later operation. Irreducible intussusception is a trying surgical problem, certain to tax the ingenuity and skill of the surgeon and the recuperative resources of the patient. The appalling mortality attendant upon the established surgical procedures has made surgeons devise newer approaches. Such a change is reflected in the experience of the Boston Children's Hospital[6] (Table 3).

Table 3. *Results of Various Types of Operation for Intussusception.*

Operation	No. of Cases	No. of Recoveries
Resection with lateral anastomosis	18	3
Open, double enterostomy	23	5
Aseptic Mikulicz's resection	14	11

McLaughlin[10] studied 200 cases in a series collected over a forty-year period (Table 4).

End-to-end anastomosis has been attended with fairly uniform failure in all reports. Dennis[11] has reported 8 successful cases, all performed by himself. Penberthy and Benson[7] described 2 consecutive failures, 1 patient dying four hours postoperatively in shock, and the other sixteen days post-

Table 4. *Results of Operation in 200 Cases of Intussusception.*

Operation	No. of Cases	Mortality
		%
Resection and anastomosis	146	67.8
Maunsell's procedure	8	100.0
Lateral anastomosis	15	26.6
Colostomy or Mikulicz's procedure	31	87.0
1937–47:		
Resection and anastomosis	48	39.0
Maunsell's procedure	3	100.0
Lateral anastomosis	7	43.0
Colostomy or Mikulicz's procedure	11	73.0

operatively of secondary bowel obstruction. Miller[12] believes that the type of operation depends upon the circumstances. Many will permit resection and anastomosis, but most often one will be fortunate in being able to perform a successful exteriorization. Barnes[13] recently suggested a neat extraperitoneal resection, in which a primary serosal layer of sutures is placed between the intussusceptum and intussuscipiens. The intussuscipiens is sutured to the peritoneal edges just below the anastomosis. When the peritoneum is closed about this site, an opening is made in the intussuscipiens, and the intussusceptum is drawn out and pegged at the anastomosis with guide sutures. The intussusceptum is removed with cautery, and an internal hemostatic layer of sutures is placed. With the guide sutures as countertraction, a small catheter is threaded back into the small bowel proximal to the anastomosis. This serves as an immediate ileostomy, decompressing the bowel proximal to the anastomosis protecting the suture line. By this means a completely extraperitoneal resection is possible.

Summary

The experience of a general hospital with both Meckel's diverticulum and intussusception in all age groups is presented.

Attention is called to one of 3 unusual cases, which is reported in detail, with successful resection and primary end-to-end anastomosis.

Some features of both Meckel's diverticulum and intussusception are reviewed.

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THE TREATMENT OF SNAKE-BITE POISONING*

A Report of Two Cases Involving the Copperhead

L. A. Chotkowski, M.D.†

KENSINGTON, CONNECTICUT

IT IS indeed a rare occasion when a physician in New England is called upon to treat a bona fide case of snake-bite poisoning although the same statement certainly cannot be made of the false alarm.

The following experience is related not primarily to suggest an ideal routine for handling poisonous snake bites, but rather to call attention to the fact that such cases can occur in New England and to suggest that there should be in the mind of every physician a rational plan for emergency and definitive therapy. The opinions of others with extensive experience in this problem are at the same time reviewed.

The poisonous reptile in these cases was the copperhead (*Agkistrodon mokasen*). It is a member of the pit-viper family, represented in the United States also by the rattler and the cotton-mouth moccasin, which is not native to New England. The only other poisonous North American snake, the coral snake, is also found only in warm climates. Although this discussion is limited essentially to matters concerning the copperhead, the bites of these three members of the pit-viper family have much in common. In a review of the literature no clinical report of a copperhead bite could be found.

Case Reports

Case 1. R. M., a 49-year-old farmer, was seen on June 7, 1947, about 15 minutes after receiving the bite of a snake, which he thought was probably a copperhead. He had been picking up kindling wood in a woodland lumber shed when the bite occurred (it was a cold rainy day in the spring, and the snake had hidden in the dry leaves under the wood pile). He had immediately applied a tourniquet to his forearm tightly enough to prevent the venous flow, but not to occlude the radial or ulnar arterial flow. On the dorsal surface of the middle phalanx of the middle finger were two puncture holes about 1 cm. apart, and 2.5 cm. distal to this were three or four smaller scratch marks. A small amount of bloody serum was oozing from the puncture holes. The patient had been squeezing his finger in this area hoping to express some of the venom, but apparently only bloody fluid was obtained. At the time he appeared in my office, only 15 minutes after the bite, edema had already developed in the involved finger extending proximally to its base and 2.5 cm. or so over the back of the hand.

Two criss-cross incisions, about 1 cm. deep, were immediately made directly over the puncture holes, and bright-red blood was obtained spontaneously and by expression. Two similar incisions were made over the edematous area proximally, and blood tinged serum was obtained. At this point, some 30 minutes after the occurrence of the bite, the tourniquet was removed because of severe pain in the hand, which was attributed to the tourniquet but in all probability was due rather to the irritating effect of the venom. The tourniquet was reapplied a few minutes later, and after about another ½ hour was discarded.

Since there was no actual proof of the identity of the snake, a search of the shed was made, and after several pieces of kindling had been removed, a copper-colored snake was uncovered. It appeared very lethargic but when teased with a stick struck viciously at it. Upon verification of the snake's identity, the farmer was removed to the New Britain General Hospital for further treatment. While searching for the snake he experienced chilliness and complained of general malaise. On admission to the hospital, about 3 hours after the bite, he was given intramuscularly 15 cc. of Lyovac,[1] a polyvalent antivenin prepared from horse serum for the treatment of any of the three North American pit-viper bites. Three thousand units of tetanus antitoxin was also given prophylactically; penicillin in doses of 30,000 units every 3 hours was started, in view of the extensive edema and the well known possibility of infection in such cases.

Two further criss-cross incisions were made proximally on the wrist. No suction was applied to the puncture wounds, which were oozing clear serum. In retrospect, thorough suction should have been attempted over the puncture wounds as well as the other incisions, and in this way perhaps some

*From the Medical Service, New Britain General Hospital.

†Junior attendant in medicine, New Britain General Hospital; clinical assistant in medicine, Hartford Hospital; attendant in medicine, New Britain Memorial Hospital.

of the subsequent edema could have been avoided. No potassium permanganate crystals or other medication was applied locally, nor was antivenin injected locally.

On admission, the vital signs were normal, and the remainder of the physical examination was essentially negative. During the night, however, the temperature rose to 100°F. by mouth. The patient felt and looked quite ill. There was considerable nausea associated with about six episodes of vomiting. His main complaint was a rather severe pain in his hand and arm lasting about 48 hours. On the following morning the edema had spread to the elbow, and by evening to the axilla. In view of this, an additional 15 cc. of antivenin was given and again repeated a few hours later. On the next day, 48 hours after the bite, the edema had spread to involve the shoulder and was extending laterally down the thorax. This area of edema over the thorax was about 20 cm. in diameter and 5.1 to 7.6 cm. in depth. The central part was characterized by a yellow and black discoloration, and the peripheral "advancing" border was warm and erythematous, fading on pressure. The left arm measured

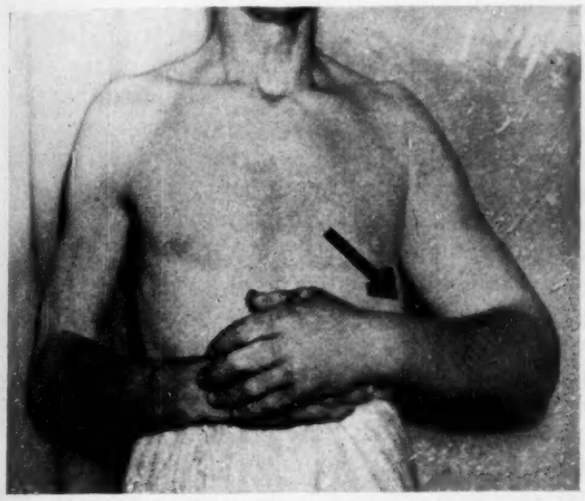

FIGURE 1. *Film Taken on the Fourth Day in Case 1, Showing Edema of the Left Arm and Thorax.*

5.1 cm. larger in circumference than the right at the midforearm, 6.3 cm. at the elbow and 7.6 cm. at the mid-arm. (Fig. 1). On the next day, the edema of the arm had begun to subside, and the arm was only 1 cm. larger at the midforearm, 3.8 cm. at the elbow and 3.2 cm. at the mid-arm. Associated with the edema was an exquisite tenderness and swelling of the epitrochlear nodes noted on the evening of admission, followed by tenderness in the axillary nodes, which were still tender even at the time of discharge on the 5th hospital day. About 96 hours after the bite, the edema of the thorax had descended to the crest of the ilium, gradually disappearing on the next day. No gangrene or slough appeared at any time, although two 1.3-cm. blisters filled with amber-colored fluid developed on the bitten finger. Edema could be detected in the involved forearm for about 3 weeks, and in the afflicted finger for about 5 weeks after the bite.

The arm was maintained on two pillows, and the patient lay in a recumbent position as tolerated. He was up and about on the 4th hospital day.

The temperature remained elevated at 100°F. by mouth for 3 days, becoming normal on the 4th; the vital signs otherwise remained normal throughout. The blood pressure was 130/80, the pulse 70, and the respirations 20.

Supportive treatment was minimal, consisting of hot wet magnesium sulfate packs to the hand, Benadryl three times a day for 2 days and a regimen of forced fluids.

On the 8th day after discharge, a mild serum sickness, characterized by urticaria and nausea, appeared and was treated satisfactorily with antihistamine drugs.

On the morning of admission the hematocrit was 51 per cent. The nonprotein nitrogen was 35 mg. per 100 cc., and the sedimentation rate 2 mm. in 1 hour. The white-cell count was 12,300, with 81 per cent segmented and 2 per cent nonsegmented forms, 15 per cent lymphocytes, and 2 per cent monocytes. The hemoglobin was 103 per cent. On the 2nd day the bleeding time was 30 seconds, and the clotting time 3 minutes. On the third day the white-cell count was 6300, with 89 per cent segmented and 3 per cent nonsegmented forms, 7 per cent lymphocytes and 1 per cent monocytes, and the hemoglobin 89 per cent. The blood serologic findings were negative. The urine on admission gave negative tests for albumin and sugar and had a specific gravity of 1.024. The sediment contained 0 to 2 pus cells and 10 to 12 red blood cells per high-power field. At the time of discharge there were still 1 to 3 red blood cells and 1 or 2 white blood cells per high-power field in the spun specimen.

CASE 2. J. L., a 19-year-old high-school student, was admitted to the emergency room of the New Britain General Hospital at 12:30 a.m. on May 2, 1949. He stated that about ½ hour before admission he had been fishing in a local reservoir, an area known to be infested with copperhead snakes. While walking about the shore of the reservoir, he felt a sudden needle-like jab in his right ankle. In the darkness it was impossible to identify the snake that had bitten him, but in view of the presence of copperheads in this area and in the absence of a rattle it was assumed that the snake was a copperhead. The patient did nothing in the way of first aid for the bite, reporting directly into the hospital. Being alone, he rode in on his bicycle, the entire trip taking about 20 minutes. While riding his bicycle, he noted pain and stiffness in the ankle and a slight chilly sensation, but no shaking chills or prostration.

On admission he appeared anxious and in some discomfort owing to the bite. Examination revealed a well developed, well nourished boy. There were two pin-point puncture wounds, approximately 1 cm. inch apart, situated on the inner surface of the right-ankle approximately 1 cm. behind the internal malleolus. There was a bloody, serous discharge from both wounds. There was also at this time, approximately 20 minutes after the bite, swelling, redness and tenderness of the entire ankle extending upward to about 7.6 cm. above the malleolus. Palpation in the popliteal space was slightly tender, and there was tenderness extending up the inner aspect of the thigh to the groin, where the lymph nodes were slightly enlarged and also tender.

The temperature was 98.6°F., the pulse 78, and the respirations 20. The blood pressure was 118/60.

Examination of the blood showed a hemoglobin of 92 per cent (14.4 gm.) and a white-cell count of 11,300, with 68 per cent segmented and 11 per cent nonsegmented forms and 21 per cent lymphocytes. The urine had a specific gravity of 1.024, with negative tests for albumin and sugar, and the sediment contained 0 to 1 pus cells and 0 to 1 red cells per high-power field. The prothrombin time on the morning of admission was 100 per cent of normal (16 seconds), and the sedimentation rate 4 mm. per hour. The blood serologic findings were negative. The nonprotein nitrogen was 42 mg. per 100 cc.

On admission to the emergency room, a tourniquet tight enough to prevent venous return was placed about the patient's thigh, and two linear incisions about 2 cm. in length were made over both puncture holes. These incisions were then irrigated with saline solution and were suctioned thoroughly for about 15 to 20 minutes hourly for the next 10 hours. The tourniquet, which at first had been applied at the thigh, was reapplied at the ankle just above the line of edema. After an intracutaneous test for horse serum sensitivity, to which the patient was negative, 15 cc. of polyvalent snake serum was injected intramuscularly. At the same time he was given 3000 units of tetanus antitoxin; 1 cc. of penicillin in oil (300,000 units) was given twice daily during the period of hospitalization. Pyribenzamine, 50 mg., was given four times daily. On admission the right ankle was 30.5 cm., the left ankle 27.9 cm., the right calf 36.8 cm., and the left calf 36.2 cm. in circumference; on the following day respective measurements were 28.6, 27.9, 36.8 and 36.8 cm. On the leg itself, which was kept flat, there appeared a yellow-blue, very tender discoloration along the lymphatic circulation of the inner aspect of the calf and inner aspect of

the thigh. This discoloration gradually became darker but less tender in the next 48 hours.

In view of the benign course that the patient was running, he was discharged from the hospital on the 3rd hospital day approximately 60 hours after admission.

At home he was allowed to be up and about, and under this treatment the residual swelling in the right ankle disappeared in about 1 week. The discoloration along the lymphatics lasted approximately 2 weeks. When last seen in the office, approximately 3 weeks after the bite, the patient felt entirely well, and the leg appeared normal. There was a moderate urticarial serum-sickness reaction 1 week after injection of the serum.

Discussion

In New England only two types of poisonous snakes are found, the copperhead and the rattlesnake, both members of the pit-viper family.[1] The term "pit" refers to a small hole on either side of the skull just in front of the eyes. The copperhead introduces its venom into its victim by way of two "hypodermic" fangs situated on the upper jaw. These lie folded flat up against the roof of the mouth when the mouth is closed, but project directly forward on a hinge-like arrangement when the mouth is open in the act of striking. These fangs are approximately 1 cm. long and are partially covered by the mucous membrane of the mouth, which peels off the teeth when the mouth is stretched open. In addition to these two fangs, there are rows of teeth on the upper and lower jaws. Although an accurate bite pattern could not be made out in the cases reported above, the two fang marks could be seen very plainly. The marks made by the lower teeth in Case 1 were also noted, but these could not be counted individually. For practical purposes, if the fang marks are absent, one can guess that either the snake was not a member of the pit-viper family — and hence, in New England, not a poisonous snake — or, less likely, the bite was superficial and no venom was injected into the victim. This point may be of major diagnostic significance when the true identity of the snake is unknown.[2]

Once the fact has been established that one is actually dealing with the bite of a venomous snake, the treatment falls into four general phases — namely, first-aid therapy, the use of antivenin, the prophylaxis of infection and the application of general supportive measures. It seems that prompt first-aid management is of considerable importance in the prognosis of these cases. Ideally, the limb is placed at rest in a dependent position, a tourniquet lightly applied proximal to the bite, and immediate incision and suction of the incision performed as soon after the bite as possible.[3, 4] This method has been accepted for years, one of the first reports appearing in the literature in 1927.[5] Multiple incisions and suctions should be made in a staggered fashion, circling the limb at higher levels as the edema advances. It is the opinion of some authorities[3, 5] that most patients are undertreated, and few, if any, overtreated. It is suggested that in a severe bite, 50 to 100 small incisions be made and suction continued for twenty minutes every two hours for thirty-six hours.[3] The tourniquet is applied lightly, since absorption of the venom is by way of the lymphatic rather than, primarily, the venous system. The copperhead bite however, usually does not appear to be fatal in adults, and such vigorous treatment may probably be deferred. Other local therapy such as the use of potassium permanganate crystals no longer seems indicated.

A polyvalent antivenin derived from horse serum and said to be effective for all North American poisonous snakes, except the coral snake, should be given immediately in the usual 15-cc. dose. It is suggested by some workers that five, ten or even fifteen doses be used in severe bites and that a single 15-cc. dose is practically of no value. (Strangely enough, however, it is believed by others that the life-saving property of this antivenin is due to the gas-gangrene antitoxin that is produced in the horse inoculated with the venom of the snake presumably containing the gas bacillus, rather than to the antivenin factor itself.) In children, since the body weight is less and the concentration of venom per kilogram thus greater, a larger dose of antivenin is necessary than in the adult. It goes without saying that since antivenin is a product of horse serum, its administration should be preceded by the usual test for sensitivity. Antivenin may be administered subcutaneously, intramuscularly or, if symptoms are severe, intravenously. It is preserved in a powdered state and must first be dissolved in distilled water. If the patient is seen within the first two hours, half the initial dose — that is, 7.5 cc. — should be injected locally. The amount of antivenin in one 15-cc. ampoule is said to neutralize the amount of venom necessary to destroy 50 pounds (22.6 kg.) of body weight.[6] On the basis of this ratio it seems that three or four ampoules contain sufficient antivenin for the ordinary case. The patient in Case 1 received three ampoules, and the patient in Case 2 only 1 ampoule. After bites from rattlesnakes and larger moccasins, in general, a larger dose is indicated.

The use of antibiotics — as in this case, penicillin — is indicated in the prophylaxis of secondary infection. Tetanus antitoxin is also indicated in view of the frequent occurrence of tetanus following snake bites.[6] Wet dressings are suggested for ulcerative areas that may develop.

General supportive care consists chiefly in the treatment of shock, if it occurs, with the use of blood or plasma, preferably blood. Since many patients have experienced either vomiting or diarrhea, fluid and electrolyte balance must be adjusted. Hemolytic anemia in severe rattlesnake bites may produce a drop of 2,000,000 in the red-cell count.[6] In Case 1 the drop in hemoglobin was ascribed to the effect of dehydration and subsequent hydration. No hemoglobinuria or jaundice was noted, although hematuria apparently due to renal irritation did

occur. As noted in the case reports, these patients required a minimum of supportive care.

The most striking evidence of a pit-viper bite is the characteristic edema, usually painful, which develops almost immediately after the bite. This is due to the effect of the injected venom. Copperhead venom is an albuminoid, the exact chemical nature of which is unknown. It is a violent irritant, producing a proteolytic and cytolytic effect on the tissues locally and a hematoxic or hemolytic effect on the red blood cells systemically. Although this venom is eventually absorbed into the lymphatics, the course of the edema suggests that its circulation and movements through the tissues occur primarily by way of the tissue spaces. This supposition of "drifting" of venom is justified on the basis of observation of these and other reported cases[3] of pit-viper bites that the edema readily ascends above known levels of communicating lymphatics — that is, into the shoulder girdle and chest wall in cases of snake bites of the hand — instead of converging into the axilla. In view of the obnoxious characteristics of this venom one might certainly hesitate before using mouth suction in removing it from the puncture wounds, particularly in the presence of gingivitis or similar oral lesions. The application of a square of rubber over the bite to protect the mouth has been suggested in emergencies. (Facial bites by the Habu snake of Okinawa in one case recently reported caused edema of the respiratory passages and respiratory embarrassment.)

Although the emergency treatment in Case 1 was inadequate, at least so far as suction was concerned, at no time in retrospect does it appear that the patient's life was in jeopardy. Statistics prepared by the Antivenin Institute of America[7] indicate that the yearly number of poisonous snake bites in this country may amount to 2000 or 3000, the death rate varying from 10 to 35 per cent. Over a twenty-year period ending in 1945, there were 2385 deaths from poisoning by venomous animals in the United States, and only 9 of these were in Connecticut, where this bite occurred.[8] These deaths include bites of spiders, centipedes and snakes of all types, and no current list of the number of fatal snake bites or of the number of deaths specifically due to the copperhead exists. In New England over a period of the last five years, there were 6 deaths due to venomous animals, none occurring in the relatively snake-free states of Maine and Vermont. Although little information could be found regarding the mortality due to copperhead bites per se, one gathers that in adults the mortality should be negligible.

Summary

The clinical course and treatment of 2 cases of poisonous snake bite (copperhead) are reported.

Only two poisonous snakes, the copperhead and the rattlesnake, both members of the pit-viper family, are found in New England, the habitat of the two other poisonous snakes in the United States, the moccasin and the coral snake, being warmer climates.

The typical pit-viper bite reveals a pattern of two prominent fang marks and is associated with immediate pain and extensive edema. If these findings are absent the bite can be considered harmless (in New England, that is).

Treatment consists essentially of the early application of a tourniquet, followed by incision and suction and the administration of three or four ampoules of antivenin. Part of this may be injected locally. The dosage varies with the size of the snake and the severity of the symptoms.

Children must be treated more vigorously than adults since the concentration of venom per kilogram of body weight is greater.

Tetanus and secondary infection should be treated prophylactically.

The prognosis for copperhead bites in adults properly treated should be good.

538 Farmington Avenue

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BENIGN GASTRIC ULCERS OCCURRING IN THE PRESENCE OF ACHLORHYDRIA*

Report of Two Cases

ELMER W. HEFFERNON, M.D.,† EVERETT D. KIEFER, M.D.,‡ AND MARTIN L. TRACEY, M.D.‡

BOSTON

OVER a period of years there has been a great deal of controversy in the literature regarding the possibility of benign gastric ulcers in the presence of an achlorhydria. Several carefully prepared reports tend to prove that achlorhydria does not exist in the presence of an active ulcer. Palmer and Nutter[1] reviewed 2200 cases of proved duodenal and gastric ulcers in 1940 and found in no case a persistent and total achylia. Bockus[2] agreed with this in his textbook stating that "true achlorhydria is not found in patients with active peptic ulcer." Washburn and Rozendaal[3] reported a series of 906 cases of pernicious anemia, in none of which an ulcer was found. Kahn[4] also reviewed 840 cases of pernicious anemia without finding any coexisting ulcers.

There has been opposing evidence presented from time to time, such as the paper by Vanzant et al.[5] in 1933, in which cases of benign gastric ulcers were found in the presence of achlorhydria. Their tests were, however, performed after Ewald meals only. Bockus and Bank,[6] in 1927, had already shown the value of checking these tests with histamine analysis. Ruffin and Dick,[7] in 1939, reported a 5.4 per cent incidence of achlorhydria in a series of 419 cases of duodenal ulcers and a 6.7 per cent incidence in 42 cases of benign gastric ulcers. However, they used only a single extraction of gastric juice three quarters of an hour after histamine, and the diagnoses were made by roentgenologic examination alone without surgical or microscopical confirmation.

A summary of the objections raised regarding the reported cases of benign ulcer with achlorhydria is as follows: a single test for free gastric acid is inaccurate; the Ewald or Rehfuss test was run for too short a time; a single histamine analysis was made when the sample of gastric juice was taken too soon after the histamine injection; proof was lacking that the histamine used was pharmacologically active; the Ewald or Rehfuss meal test was not confirmed by a histamine analysis; the gastric analysis was not done at the time the ulcer was known to be active; and the diagnosis of benign ulcer was not absolutely confirmed by microscopical examination. Too frequently, patients are seen with gastric ulcers that have been diagnosed clinically, roentgenographically and pathologically (gross) as a benign ulcer only to discover from microscopical examination that cancer is present.

A recent paper by Ricketts and his associates[8] pointed out that, by definition, the term "peptic ulcer" implies the presence of both free hydrochloric acid and pepsin. It is proved that peptic activity occurs at an optimum hydrogen ion concentration, which requires acid present to attain this concentration. It is also a more or less accepted belief that "peptic ulcers" are caused by the action of acid and pepsin on a mucosa that has been altered in some manner and is now susceptible to this digestive action.

With all these points in mind we consider the following 2 cases worth reporting since both patients had a persistent achlorhydria — by both Ewald meal and histamine tests with the histamine test carried out to seventy-five minutes on each occasion. Clinically, the histamine used in the tests appeared to be pharmacologically active. Both patients had clinical courses indistinguishable from those of patients with benign gastric ulcers (so-called "peptic ulcers"). Pathologically, on gross and repeated microscopical examination, Dr. William A. Meissner found only benign ulceration. In both cases other causes of ulceration of the stomach such as trauma, gastritis of specific origin, syphilis, tuberculosis, foreign body and local vascular disorders, could be excluded; arteriosclerosis was present generally, but no local changes were found in the vessels in the pathological specimens.

CASE REPORTS§

CASE 1. A 69-year-old, retired man entered the Lahey Clinic on October 5, 1948, complaining of epigastric pain for a period of 3 or 4 years occurring 3 or 4 hours after meals and sometimes relieved by food and by sodium bicarbonate. There had been times when this pain required morphine by injection for relief. He had never been free from the pain for more than 2 days at a time during this period. His appetite had been poor for the past 4 or 5 months, and he had noted some difficulty in swallowing meat. He complained of belching and flatulency for a period of years, and for the past few months had vomited about once a week. He had had one black stool about 6 months previously, and he had been taking no medication at the time. He complained of constipation over a period of years for which he had been using daily laxatives. A 17-pound weight loss had occurred during the past year.

A review of the systems, past history and family history were noncontributory.

Physical examination revealed that the patient weighed 86 pounds. He was cachectic and pale. There were beginning cataracts of both eyes. The tongue was smooth and fairly

*From the Department of Gastroenterology, Lahey Clinic.

†Physician, Department of Gastroenterology, Lahey Clinic.

‡Physician, Department of Gastroenterology, Lahey Clinic; associate physician, New England Deaconess and New England Baptist hospitals.

§In both cases the gastric analysis (unless specified as a histamine analysis) was done after an Ewald meal consisting of plain soda crackers and water.

moist, and some senile emphysema was present; the posture was poor, and there was coldness of the extremities. Dorsalis-pedis pulses were not obtainable, and moderate peripheral arteriosclerosis was present.

The blood pressure was 130/70, and the pulse 80.

Urinalysis was negative. Examination of the blood disclosed a red-cell count of 4,150,000, with a hemoglobin of 14.1 gm. (90 per cent), and a white-cell count of 6900, with a normal differential. The blood sedimentation rate was 23 mm. per hour, and the blood Hinton reaction was negative. A stool examination revealed no occult or gross blood. The nonprotein nitrogen was 29 mg., and the total protein 5.6 gm. per 100 cc., with an albumin-globulin ratio of 1.8 to 1. The chloride was 96 milliequiv. per liter, the cephalin flocculation ++, and the blood phosphorus 2.7 mg. per 100 cc. A gastric analysis done after an Ewald meal on October 6 revealed no free acid with a total acidity of 10 units. Gastric analysis after an Ewald meal on November 16 disclosed no free hydrochloric acid, with a total acidity of 2 units. Gastric analysis carried out on November 16 after histamine revealed no free hydrochloric acid throughout, and no acidity was found. (The test was carried out for 75 minutes.) Proctoscopic and barium-enema examinations were negative.

A roentgenogram of the upper gastrointestinal tract showed a gastric ulcer measuring about 1 cm. in diameter projecting from the lesser-curvature side of the stomach at the junction of the cardia and body. There was an hour-glass appearance below this. The rest of the upper gastrointestinal study was negative.

In view of the patient's age, clinical history, roentgenologic findings, achlorhydria and poor relief under medical management, a preoperative diagnosis of cancer of the stomach was made, and he was admitted to the New England Deaconess Hospital on November 15.

During his hospital stay a gastric resection was carried out. At operation an ulcer of the lesser curvature of the stomach at the junction of the upper and middle thirds was found surrounded by multiple adhesions. It was impossible to tell whether this was benign or malignant grossly. The operation consisted of partial gastric resection and an end-to-side retrocolic gastrojejunostomy done by the Hofmeister technic.

Microscopical examination on multiple sections (at least 30) of the specimens revealed no evidence of any malignant degeneration, and a diagnosis of benign ulcer of the stomach was made. (Thirteen lymph nodes were also examined and found to be normal.)

Postoperatively, the course was complicated by upper abdominal pain, vomiting and pain in the chest. The medical consultant thought that the patient also had arteriosclerotic heart disease, chronic pulmonary emphysema, chronic bronchitis and malnutrition. Digitalis was given, and potassium iodide administered intravenously, and under this therapy he rapidly improved. He was discharged from the hospital on December 11, improved, on a bland diet, five small feedings a day, accessory vitamins and proper rest.

He was subsequently seen on January 11, 1949, when he weighed 88½ pounds and still complained of some pain in the epigastrium after meals and some diarrhea. A recent letter from him informs us that he has no pain now and is gaining weight.

Case 2. A 64-year-old married coppersmith was first seen at the Lahey Clinic on January 28, 1944. He complained of epigastric pain of 1 year's duration occurring about 1 hour after meals and awakening him at 1 or 2 a.m. The pain was relieved by alkali and cream. He also complained of the feeling of a lump in the right upper abdominal quadrant and of chronic constipation over a period of years requiring frequent cathartics. The epigastric pain was periodic, leaving him for weeks or more with complete freedom. A roentgenogram of the upper gastrointestinal tract elsewhere had disclosed an ulcer.

A review of the system, and the past and family histories were noncontributory.

On physical examination the patient weighed 138 pounds. Examination of the abdomen revealed tenderness, with some muscle guarding on the right side. The right lobe of the prostate was slightly enlarged. The remainder of the physical examination was within normal limits.

The blood pressure was 110/60, and the pulse, respiration and temperature were normal.

Examination of the blood at this time revealed a red-cell count of 4,820,000, with a hemoglobin of 15.1 gm. (97 per cent), and a white-cell count of 5500. The blood Hinton reaction was negative. Gastric analysis revealed 60 per cent food content, no free hydrochloric acid, a total acid of 8 units and no occult blood. Examination of the urine showed slight albuminuria, no sugar, a specific gravity of 1.030, an acid reaction and no formed elements.

Roentgenograms of the large intestine and gall bladder were completely normal. A roentgenogram of the upper gastrointestinal tract revealed a normal esophagus, but high on the lesser curvature of the stomach was a 1.5-cm. outpocketing, with some thickening and distortion of the rugal pattern of the fundus. This was interpreted clinically as a gastric ulcer, probably malignant because of achlorhydria.

In view of this the patient was admitted to the New England Baptist Hospital on February 7. An exploratory laparotomy was performed, and he was found to have a benign gastric ulcer. Biopsy specimens of the ulcer and the lymph nodes around the omentum were normal microscopically. Postoperatively, atelectasis of the left lower lobe of the lung developed, with associated pneumonitis. He recovered from this and was discharged from the hospital on February 25. During his hospital stay he had been managed on a strict ulcer type of dietary management, rest, antacids and antispasmodics.

After this hospitalization he was seen periodically. In April a gastric analysis after an Ewald meal still revealed no free hydrochloric acid, with a total acid of 11 units. Examinations of the blood and urine were negative. Roentgenograms of the upper gastrointestinal tract at that time showed that the gastric ulcer measured only 1 cm. in its greatest extent.

The patient was also seen in July, when a free hydrochloric acid of 2 units was found, with a total acid of 8 units on gastric analysis. The blood was normal, and a repeat gastrointestinal series at this time revealed that the ulcer had completely healed.

In January, 1945, a gastric analysis demonstrated no free hydrochloric acid and a total acid of 8 units. The blood was normal, and a roentgenogram of the upper gastrointestinal tract revealed no abnormalities.

He was seen again in September, 1947, complaining of a recurrence of epigastric distress, and again physical examination was negative; the blood pressure was 120/80. At this time gastric analysis showed no free hydrochloric acid and a total acid of 8 units; the blood was normal, and examination of the urine negative. A roentgenogram of the upper gastrointestinal tract revealed prepyloric and antral spasm but was otherwise normal.

The patient returned to the clinic in October, when a histamine gastric analysis was carried out. A specimen was taken 15 minutes, 30 minutes, 45 minutes, 1 hour and 1¼ hours after histamine. The test revealed no free hydrochloric acid with a total acid of 6, 8, 4, 10 and 12 units, respectively. Roentgenograms of the stomach disclosed narrowing of the antrum of the stomach but were otherwise normal. Examination of the blood at this time was normal.

The patient was again seen in December, when a gastric analysis demonstrated no free hydrochloric acid and a total acid of 15 units. The blood was normal, and a roentgenogram of the upper gastrointestinal tract revealed no abnormalities.

In January, 1948, gastric analysis demonstrated no free hydrochloric acid and a total acid of 5 units. The blood was normal. In March the blood was still normal. Roentgenograms of the upper gastrointestinal tract revealed recurrence of an ulcer on the lesser curvature of the stomach, with a possible filling defect at the base of the ulcer. The patient was therefore readmitted to the New England Baptist Hospital on April 18, and a high subtotal gastric resection was carried out. In view or the fact that past history included achlorhydria, the specimen was examined with extreme care microscopically, but no evidence of cancer was found and therefore the presence of a benign gastric ulcer with a chronic gastritis was confirmed. Lymph nodes taken from the region at operation were also negative for malignant change. He was discharged from the hospital on May 4, after an uneventful postoperative course, although a further diagnosis of Paget's disease of the pelvis was made at this time.

The patient was readmitted to the hospital on May 18 because of vomiting and lack of appetite. Levine-tube drain-

age of the stomach was instituted for 24 hours, after which he had again responded well and was discharged on May 27.

In October he returned for examination. He had done well except for fainting spells, which the neurosurgical consultant thought were probably on the basis of cerebrovascular disease, but he had had no further gastrointestinal complaints. The blood was normal and a gastric analysis revealed no free hydrochloric acid and a total acid of 20 units. A barium meal demonstrated a normally functioning, subtotally resected stomach and gastroenterostomy.

Discussion

If we take shelter in the definition of peptic ulcer that automatically excludes any benign ulcer with an accompanying achlorhydria, further discussion is unnecessary. However, if we admit the possibility that peptic ulcers may occur under these circumstances it adds one more item to the general problem of peptic ulcer. We consider the 2 cases reported to be clinically indistinguishable from benign "peptic ulcers," and yet we have fairly well proved the existence of an achlorhydria in both. We have also excluded as far as possible any specific etiology for the gastric ulcers. It is interesting to note that in both cases parietal and chief cells were found in the gastric mucosa microscopically.

Summary

Reports concerning the pros and cons of ulcer and achlorhydria are briefly enumerated.

Two cases of benign active gastric ulcers in the presence of persistent achlorhydria are reported.

Pathological confirmation was obtained through the kindness of Dr. William A. Meissner, of the Department of Pathology, New England Deaconess Hospital.

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THE EFFECTS OF A SINGLE DOSE OF 2000 UNITS OF PROTAMINE ZINC INSULIN TAKEN BY A DIABETIC PATIENT WITH SUICIDAL INTENT*

Alfred Vogl, M.D.,† and Sol H. Youngwirth, M.D.‡

NEW YORK CITY

THE effects of exceedingly large doses of protamine zinc insulin are known chiefly from patients who have taken excessive amounts by error.[1] The literature, however, also lists 2 cases in which huge quantities were taken with suicidal intent, 490 units in the first case and "one bottle" in the other.[2] These observations indicate that overdosage with protamine zinc insulin is characterized by a definite sequence of symptoms.

Since the effect of protamine zinc insulin on the blood sugar level develops much more slowly than that of unmodified insulin, there is a considerable initial period during which the compensatory mechanisms (chiefly increased liberation of epinephrine) are able to maintain a more or less adequate blood sugar level by mobilizing the available glycogen in the liver.[1, 3] However, once the glycogen stores are exhausted, the production of epinephrine is no longer of any avail, and, with the further uptake of insulin from the protamine zinc depot, hypoglycemia becomes clinically manifest and progressively more severe. If the hypoglycemic state is treated at this point with oral or parenteral administration of carbohydrate the blood sugar level may be raised to normal or close to normal levels, but this effect is very transient. The continuous liberation of insulin in the absence of glycogen stores in the body necessarily leads to recurrent hypoglycemia soon after each therapeutic administration of sugar until the protamine-zinc-insulin depot has been depleted.[1]

Without adequate treatment, therefore, the hypoglycemia following overdosage with protamine zinc insulin is characterized by its intractability, severity and duration, and it is apt to lead to irreversible tissue changes (particularly in the brain[3-5] and myocardium[6]) comparable to those found in prolonged anoxia.

Coma and vomiting have been a more prominent feature of the hypoglycemia due to protamine zinc insulin than of that caused by regular insulin.[1]

A male diabetic patient who took 2000 units of protamine zinc insulin in a single dose afforded us the opportunity of observing some of the effects of such a large dose of insulin on the carbohydrate metabolism.

*From the Third Medical (New York University College of Medicine) Division of Bellevue Hospital.

†Assistant professor of clinical medicine, New York University College of Medicine; associate visiting physician, Bellevue Hospital.

‡Assistant resident in medicine, Bellevue Hospital.

Case Report

The patient was a 63-year-old man who had had diabetes for about 10 years and who required 40 units of protamine zinc insulin daily. For the preceding few years he had also been treated for arteriosclerotic heart disease with anginal syndrome. For many years he had been unable to work because of poor vision. He became depressed, and 1 year previously he had attempted suicide with insulin.

On the morning of November 2, 1948, the patient received his usual injection of 40 units of protamine zinc insulin. At approximately 5 p.m. on the same day, the patient announced to his wife that he had a little while previously injected into himself the contents of "three bottles" of protamine zinc insulin with the intention of killing himself. The wife found the three empty bottles, two of 80 and one of 40 units per cubic centimeter (representing a total of 2000 units), the contents of which the patient claimed to have injected subcutaneously. At this time he showed no unusual symptoms. A doctor who was called at once declared treatment unnecessary.

During the night the patient had a few episodes of perspiration and apprehension, not different from the hypoglycemic symptoms occasionally experienced in the past. His wife treated them successfully with fruit juice and frequent feeding.

On the following morning he was taken to a hospital, where no sign of insulin reaction was found and, after several hours, he was transferred to the psychiatric division of Bellevue Hospital because of his repeated suicidal attempts. Immediately prior to his transfer he became apprehensive and started to perspire. He was given 40 cc. of 50 per cent glucose solution intravenously, and drank a cup of orange juice; immediate improvement followed.

On admission to Bellevue Hospital at 5 p.m. on November 3 he was fully conscious and oriented and asked for something to eat. He was sweating moderately and appeared very apprehensive but in no acute distress. The skin was cool, and the pulse very rapid and irregular. He was immediately given 50 cc. of 50 per cent glucose intravenously. Sweating and apprehension disappeared promptly, the pulse rate slowed, and he appeared comfortable and spoke rationally. Physical examination at this time showed a temperature of 98.4°F., a pulse of 64 and respirations of 16. The blood pressure was 130/68. Fundoscopy revealed diabetic retinopathy. The heart was enlarged. The chest was clear. The abdomen was soft. On both thighs were many injection marks. Neurologic examination was negative. The urine on admission was free of sugar and acetone.

The patient's course in the hospital was characterized by great difficulty in attaining and the inability to maintain a normal blood sugar level. This persisted for 6 days in spite of almost continuous oral and parenteral administration of huge amounts of carbohydrates. During this period there was a persistent tendency to lapse into hypoglycemia whenever the therapeutic efforts were relaxed.

Until 7 a.m. of the 2nd day — that is, during the first 38 hours after the insulin had been taken, the symptoms were mild and relatively easily controlled. This period included the first 14 hours at Bellevue Hospital, when 320 gm. of carbohydrates was given — 295 gm. by mouth and 25 gm. by vein.

After this 38-hour period had passed, however, the patient started to vomit and rapidly went into coma. At this time the blood sugar was less than 10 mg. per 100 cc.; 50 cc. of 50 per cent glucose was at once given intravenously and followed by an intravenous infusion of 12.5 per cent glucose in water. About 2 hours later the patient regained consciousness and was able to take food by mouth. He remained comfortable, except for a few episodes of sweating, although the blood sugar did not rise above 33 mg. per 100 cc. that afternoon.

The blood sugar was still 54 mg. per 100 cc. at 10 p.m. on the 3rd day. During the 15-hour period from the onset of coma at 9 a.m. until midnight, he received a total of 275 gm. of glucose intravenously and 300 gm. of carbohydrates orally in the form of sweetened fruit juices.

His condition became critical during the night and the following morning, when hypoglycemia was most profound and the largest amounts of carbohydrate he was to receive on any day were required. The intravenous infusion of glucose had inadvertently been stopped, probably for about 1 hour before 2 a.m. At this time he was found vomiting and perspiring and rapidly lapsed into coma. After 50 cc. of 50 per cent glucose had been given intravenously he recovered quickly. The infusion was restarted at the same time. At 7:30 a.m. the infusion was stopped again. About 1 hour later the patient began to vomit, became deeply comatose, had a rapid, irregular pulse and developed pulmonary edema. The blood pressure was 180/80. He was again given 50 cc. of 50 per cent glucose intravenously but this time without response. The blood sugar of a specimen drawn a few minutes after the intravenous injection of glucose was reported as less than 10 mg. per 100 cc. The serum potassium was 3.5 milliequiv. per liter at this time. In view of the pulmonary edema it was believed that infusions should not be continued for the time being, and glucose was given in the form of a 50 per cent solution, 50 cc. at a time for a total of 260 gm. between 9 a.m. and 9 p.m. In addition, 1800 cc. of milk and eggnog, containing 150 gm. of carbohydrates, was fed to the patient through a Levine tube. He was rapidly digitalized and given a transfusion of 500 cc. of blood. After 4 hours of treatment, his coma lightened, but he remained confused and drowsy for the rest of the day. Pulmonary edema cleared gradually. During this period of generous oral and parenteral administration of glucose the urine remained almost consistently sugar free, and the blood sugar was 35 mg. per 100 cc. at 12:40 p.m.

After 6 p.m. on the 4th day tube feeding was discontinued because of abdominal distention. Five hundred cubic centimeters of whole blood was given slowly. By 9 p.m. it was considered safe to resume glucose infusions; a 22 per cent solution was used for this purpose, and it was supplemented on two occasions by 50 cc. of 50 per cent solution injected intravenously. By midnight the urine showed a ++ test for sugar.

The patient had received a total of 920 gm. of carbohydrate (680 gm. by vein and 240 gm. orally) during the preceding 24 hours. But shortly after midnight the urine was again sugar free, and restlessness and perspiration reappeared.

On the next morning he experienced mild hypoglycemic symptoms. At 8 a.m. the blood sugar was 50 mg. per 100 cc. The 22 per cent intravenous glucose drip and the Levine-tube feedings were continued until 4 p.m., when the urine samples contained increasing amounts of sugar.

On the 5th day the patient's sensorium appeared clear, and he was able to take food and was started on a diet containing 180 gm. of carbohydrate. His urine remained sugar free the rest of the day.

On the 6th day the patient again appeared drowsy most of the time. The blood sugar was found to be 30 mg. per 100 cc. at 9 a.m., even though he had been receiving carbohydrate feedings during the night. During the day his condition remained unchanged, and the urine was free of sugar on a diet containing 260 gm. of carbohydrate.

He was, therefore, again started on intravenous 22 per cent glucose at 6 p.m. on the following day. Soon afterward he was found to be excreting increasing amounts of sugar (a ++ to +++ test) in the urine. The infusion was stopped at 6 a.m. At 10 a.m. the blood sugar was 210 mg. per 100 cc.

From the 8th day on, the patient was well oriented and took his full diet containing 180 gm. of carbohydrate. During this period the urinary sugar varied from 0 to +++, and the blood sugar remained around 200 mg. per 100 cc.

On the 13th day it was decided to start the patient on insulin again; he received repeated small doses of regular insulin and was gradually returned to protamine zinc insulin.

Two weeks later the diabetes was well controlled on 40 units of protamine zinc insulin. The patient's physical and mental condition was quite satisfactory by this time; he was completely oriented and according to the statement of his wife had not changed in any way.

An electrocardiogram taken during the coma and pulmonary edema on the 3rd day showed sinus tachycardia (a rate of 144 per minute), with occasional premature ventricular contractions and elevated ST segments in Lead 2 and 3. Twelve days later, when the procedure was repeated, the rhythm was regular and the ST segments isoelectric.

In summary, after a single hypodermic injection of 2000 units of protamine zinc insulin this diabetic patient showed severe manifestations of hypoglycemia for 6 consecutive days with the greatest severity on the 3rd day. In this period he received almost 3000 gm. of carbohydrate (1425 gm. by

vein and about 1400 gm. by mouth), but the urine remained sugar free most of the time and the blood sugar never exceeded 54 mg. per 100 cc. Twelve days elapsed before it became necessary to reinstitute insulin therapy although he had previously required daily injections of 40 units.

Discussion

This case illustrates the problems created by an unusually great overdosage of protamine zinc insulin. The initial absence or paucity of symptoms in no way minimizes the seriousness of the situation. When a person is known to have received or is suspected of having received an excessive amount of protamine zinc insulin, he must be regarded as an emergency [1, 7, 8] and kept under careful observation lest severe hypoglycemia develop abruptly and become increasingly difficult to control, if not fatal.

The experience with this patient also showed that prompt improvement of symptoms after carbohydrate administration must not give rise to a false sense of security. The response to the administration of glucose in such a case is bound to be quite transient since the liberation of insulin from the injected depot takes place over a long period, whereas the glycogen stores in the body are depleted during the early phases of hyperinsulinism. It is therefore of prime importance to administer a continuous supply of readily available carbohydrate to such patients.[7] Oral feedings can be depended upon only if the patient remains fully conscious, a nurse is in constant attendance, and the patient does not vomit. If the patient is unconscious, full reliance cannot be placed on feeding through a Levine tube since gastric atony with retention may occur in this state.[1] Continuous intravenous drip infusion is therefore preferable during the critical phase. The attempt to give a sufficient amount of carbohydrate by this means is, of course, always fraught with the danger of flooding the circulation to a degree at which pulmonary edema results, as occurred in the case reported above. This difficulty can probably best be overcome by the use of a highly concentrated solution. A 22 per cent solution of glucose in water, occasionally supplemented by the further intravenous injection of 50 cc. of a 50 per cent solution, was finally resorted to.

It should be emphasized that on the third day, during the most profound phase of hypoglycemia, a brief interruption of the parenteral supply of glucose led to a virtually complete disappearance of sugar from the circulating blood and to deep coma from which recovery was relatively slow. From the experiences in cases reported in the literature it may be assumed that serious organic damage would have resulted if such a degree of hypoglycemia had been allowed to persist longer.[3, 4, 9, 10] Conversely, the patient's recovery without any demonstrable cerebral or cardiac damage may be attributed to the almost continuous maintenance of the blood sugar above levels injurious to brain and heart by means of intravenous infusions and frequent feedings and by the intravenous administration of additional concentrated solutions of glucose whenever, in spite of all efforts, the blood sugar dropped below critical values. The recovery is the more remarkable since the patient had signs of pre-existent generalized arteriosclerosis with symptoms of circulatory (and particularly coronary) insufficiency. Other patients have been known[4, 9, 11-13] to develop permanent brain damage of varying, occasionally extreme, severity after prolonged hypoglycemia, even though it resulted from far smaller doses of insulin.

It is generally recognized that the action of individual therapeutic doses of protamine zinc insulin may extend well beyond a twenty-four-hour period, even into the third day.[8] In fasting patients single injections have maintained hypoglycemic levels for as long as forty-eight to seventy-two hours.[14] In animal experiments, a single injection of protamine zinc insulin has produced hypoglycemia of thirty hours' duration in rats and of three to five days' duration in dogs.[15] The larger the dose given, the more prolonged the effect. The same statement, incidentally, holds for unmodified insulin, with which the duration as well as the intensity of the effect also varies in proportion to the size of the dose given.[16, 17] To our knowledge, hypoglycemia of six days' duration, as reported above, has not been noted after a single injection of insulin. However, there is no basis for comparison, since there is no case on record in which such a large quantity of insulin was received in a single dose. The knowledge that the amount of insulin will directly determine the duration of its effect assumes practical importance whenever a large dose of protamine zinc insulin is given either in error or by design. Any prediction about the course of events in such cases, particularly regarding the duration of the critical period and the length of time during which continuous, vigorous therapy will be required, obviously cannot be based on experience with the customary doses of insulin, but must be estimated according to the amount administered. Periods of hypoglycemia of sixty hours, as observed by Aitkin,[18] after 100 units of protamine zinc insulin, and of one hundred and forty-four hours, as seen in our case after 2000 units of protamine zinc insulin, could serve as two indexes that may be useful for calculation in cases of this kind.

The question may be raised why the patient received a transfusion of whole blood on the third day of treatment. The indication was based on Joslin's[7] opinion that a transfusion of fresh blood may be able to supply the respiratory enzymes, which appear to be inhibited during hypoglycemia.[19] It may also assist in the restoration of a disturbed electrolyte balance.

The electrocardiographic findings are noteworthy. During the episode of greatest hypoglycemia with coma and pulmonary edema, the findings included a sinus tachycardia (a rate of 144 per minute), premature ventricular contractions and definite elevation of the ST segments in Lead 2 and 3. At this time the blood potassium level was normal.[20, 21] Twelve days later the ventricular rate was 64 per minute, and the ST segments isoelectric. These changes are at variance with those observed by others during hypoglycemia.[22-24]

Summary

A case in which suicide was attempted with a single injection of protamine zinc insulin is reported. The patient had few symptoms during the first twenty-four hours but, in spite of vigorous and continuous treatment, developed increasingly severe hypoglycemia, with periods of coma on the second and third days, and recurrent manifestations of milder hypoglycemia, with a blood sugar of 30 mg. per 100 cc. up to the sixth day. During this period he received close to 3000 gm. of carbohydrate and yet was unable to maintain or even approach a normal blood sugar level. The blood sugar, however, was kept above critical values (at 30 to 50 mg. per 100 cc.) most of the time, and the patient suffered no demonstrable permanent damage.

The possible causes for the delayed appearance of symptoms, the severity of the hypoglycemia and the difficulty in maintaining an adequate blood sugar level after an excessive dose of protamine zinc insulin are discussed. It is stressed that the duration of the hypoglycemic effect increases in proportion to the size of the dose. This fact may account for the extremely protracted course of hypoglycemia in the case reported, exceeding that in any other known case on record.

The therapeutic urgency in this type of case is emphasized, in particular, the necessity of continuous and prolonged intravenous administration of carbohydrate.

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LIPOATROPHY FOLLOWING THE INJECTION OF INSULIN*

A Method of Control

WILLIAM S. COLLENS, M.D.,† LOUIS C. BOAS, M.D.,‡ JAMES D. ZILINSKY, M.D.,‡ AND JEROME J. GREENWALD, M.D.‡

BROOKLYN, NEW YORK

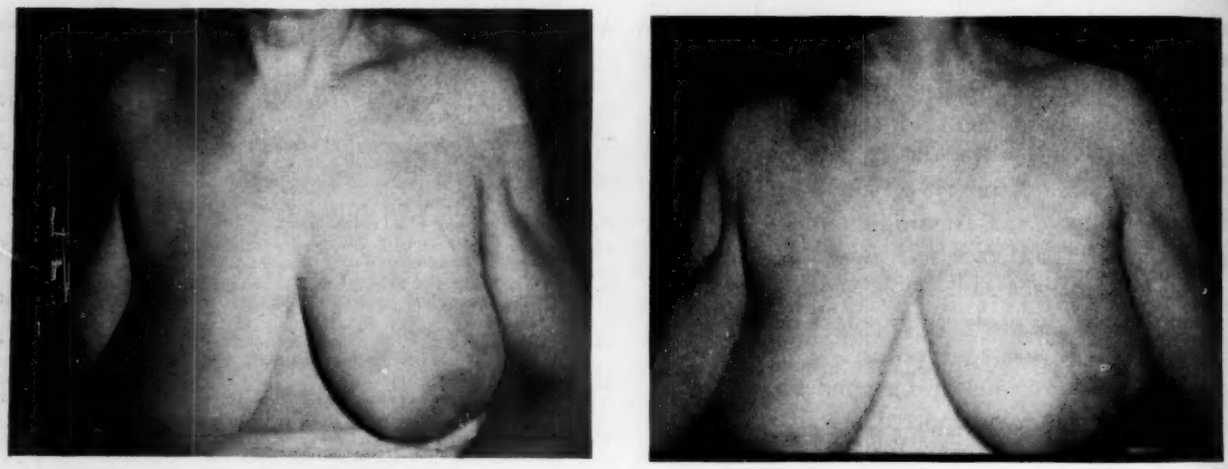
AMONG the many problems that have arisen since insulin was introduced as an agent in the treatment of diabetes mellitus is one concerned with the development of local fat atrophy at the site of insulin injections. Although of relatively infrequent occurrence, the problem has always proved to be very distressing to the patient because of the considerable amount of disfigurement it produces.

Insulin lipoatrophy is a condition in which the subcutaneous fat disappears at the site of the insulin injection, leaving a depression in the skin (Fig. 1 and 2). It develops in some cases when the insulin is injected at the same site over a period of as little as four weeks. In other cases it may take months to appear. It may occur after the use of any type of insulin and is unrelated to the dosage and concentration.

The cause of this lipoatrophy is unknown. There has been no satisfactory explanation to account for the complication although several theories have been propounded. Among the possible factors considered responsible are the cresols used as a preservative of insulin, alcohol and its denaturants used in sterilizing syringes and needles, injury to fat cells following the introduction of the hypodermic needle, possible lipolytic ferments present in insulin and possible nerve injury.

On the basis of the possibility that this condition might be an allergic phenomenon, some of the patients in our clinic were subjected to skin tests by the intradermal injection of various commercial brands of insulin. There was no uniformity in the reaction, some being negative and others mildly positive. Such reactions were also obtained in other diabetic patients who revealed no manifestations of lipoatrophy. It was therefore not possible to come to any conclusion regarding the existence of any unusual sensitivity in these cases. Furthermore, there are no experimental or clinical data available to shed any light on the mechanism responsible for the condition.

A successful method for the treatment of lipoatrophy is presented. This method was conceived as the result of a patient's suggestion. A young woman, twenty-three years of age, who had been diabetic since the age of twelve, had developed multiple areas of lipoatrophy on the arms, thighs,



A B

FIGURE 1. *Case of Insulin Lipoatrophy Involving Both Arms.*
A *shows appearance before treatment.* B *shows appearance two months after treatment of the left arm.* (*Note the marked improvement; the right arm was used as a control and was not treated.*)

*From the Diabetic Clinic and the Medical Services, Maimonides Hospital.

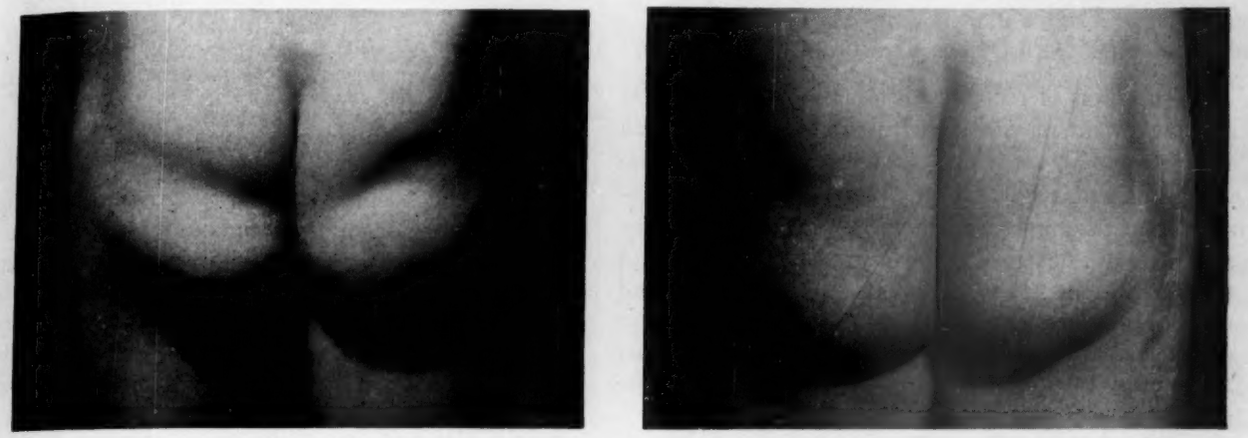
†Associate attending physician and chief of Diabetic Clinic, Maimonides Hospital.

‡Assistant physician, Diabetic Clinic, Maimonides Hospital.

abdomen and buttocks. In desperation and not knowing where else to inject her insulin, she inquired about the possible harm that might come from injecting insulin into the lipoatrophic areas. There did not appear to be any serious objection to reinjection of these depressed areas. The patient returned one month later, and it was surprising to find that one atrophic area, which the patient had not injected for two years, had, after repeated daily injections, filled out and returned to its normal configuration.

As a result of this experience, the patient has since reinjected all the scooped out depressions and has practically recovered from all her deformities.

We have since advised 6 other patients suffering from insulin lipoatrophy to inject their daily insulin doses repeatedly into the deepest portion of the depression and in all these cases have seen, in one month's time, striking complete recovery from the deformities.



A B

FIGURE 2. *Case of Insulin Lipoatrophy in a Ten-Year-Old Boy Involving Both Buttocks.*
A *shows appearance before treatment.* B *shows appearance six weeks after treatment. (Note almost complete recovery.)*

SUMMARY

A method for the successful treatment of insulin lipoatrophy is briefly presented.

MEDICAL PROGRESS

MEASURES USED IN THE PREVENTION AND TREATMENT OF CARDIAC ARRHYTHMIAS (Concluded)*

ARTHUR J. LINENTHAL, M.D.,† AND A. STONE FREEDBERG, M.D.‡

BOSTON

QUINIDINE (AND OTHER CINCHONA ALKALOIDS)

Quinidine is of recognized value in the prevention and treatment of various cardiac arrhythmias, such as paroxysmal ventricular tachycardia and paroxysmal auricular fibrillation. However, there is considerable disagreement about the exact indications and contraindications, the nature and frequency of toxic reactions, the routes of administration and the dosage schedules of the drug. Since there is so much confusion surrounding the use of quinidine, the pertinent available information has been assembled and is discussed in some detail.

Physiologic Disposition

Knowledge of the fate of quinidine in man has been obtained by sensitive, accurate and specific analytical methods developed in the past few years.[99-108] The relation between oral dosage and the resulting plasma concentration has been studied, and information obtained on absorption, distribution, excretion and metabolic alteration, which combine to determine the level of quinidine in the blood.

Relation of oral dosage to plasma concentration. Within fifteen minutes of a single oral dose of 0.2 to 1.0 gm. of quinidine sulfate the alkaloid can be detected in the plasma. Maximum levels are reached in one to three hours and may be maintained for two or three hours.[107, 109] The subsequent fall is at first fairly rapid and then slower. Approximately 50 per cent and 25 per cent of the peak value remain after eight and twelve hours respectively. At the end of twenty-four hours only a trace of quinidine can be demonstrated in the plasma. Average peak plasma concentrations after single doses of 0.2, 0.4, 0.6 and 1.0 gm. are, respectively, 0.8, 1.3, 2.0 and 2.7 mg. per liter.[64, 107, 110]

When the same dose of quinidine sulfate is administered at two-hour intervals — that is, at the time of the peak response to the preceding dose — the plasma concentration increases, but the increase becomes smaller and smaller with each successive dose, and the curve levels off after four or five doses. Presumably, at this point, the rate of absorption balances the combined rates of excretion and metabolic alteration.[64, 107]

When the same dose is repeated at intervals of six, eight or twelve hours, the peak level after several days is not significantly greater than that after the first dose. The maximum concentration is slightly lower when the doses are given every twelve hours than when they are given every six to eight hours; with the more frequent administration the concentration is maintained at a higher level in the period between peaks. When the size of the dose is increased, the height of the peak is raised appreciably.[64, 107] The size of the individual dose is the most important factor in obtaining a high plasma level of quinidine.[64] Cumulation is minimized by rapid elimination, and, therefore, the total daily dose and the total weekly dose are of little significance.

Relation of parenteral dosage to plasma concentration. Limited information is available regarding the plasma concentration of quinidine following *intramuscular* administration.[64] Initial absorption is more rapid than after oral administration; the peak level is no higher and does not occur significantly earlier. The rate of disappearance and the time required for complete disappearance from plasma are the same as those after oral administration. As would be expected on the basis of these findings, the plasma concentration following repeated intramuscular doses follows the same pattern as that after repeated oral doses.[64]

We are not familiar with any data on the plasma levels of quinidine following *intravenous* administration of the drug in man.

Absorption. Quinidine is practically completely absorbed from the human gastrointestinal tract. After oral administration of repeated doses, less than 5 per cent can be recovered from the stools.[111, 112] The rapidity with which the drug can be detected in the blood suggests that absorption must at least begin in the stomach. Absorption also occurs from the intestinal tract as evidenced by studies with enteric-coated tablets of quinidine sulfate, which, presumably, pass through the stomach unchanged. Peak plasma concentrations following the enteric-coated preparation are comparable to those observed after the administration of uncoated tablets.[64]

Distribution. Distribution studies in dogs have shown no unusual concentration of quinidine in the

*From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Departments of Medicine and Pharmacology, Harvard Medical School.

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†Instructor in medicine and instructor in pharmacology, Harvard Medical School; associate in medicine and associate in medical research, Beth Israel Hospital.

‡Associate in medicine, Harvard Medical School; visiting physician and associate in medical research, Beth Israel Hospital.

myocardium. Quinidine concentrations in various tissues range from two to thirty-nine times the plasma concentration,[113, 114] and the level in auricular and ventricular muscle falls within this range.[113] The time at which the highest quinidine concentration is reached, as well as the subsequent fall in concentration in cardiac muscle and other tissues, is correlated with plasma-level changes.[113] These observations indicate a ready equilibrium between the plasma and tissues of the dog.

Few observations have been made in man of the extent to which quinidine is concentrated in various tissues. In normal persons receiving single and repeated doses of the drug the concentration of the quinidine in the cellular elements of the blood varies from 0 to 80 per cent of the plasma level.[64]

Excretion and metabolic alteration. The total urinary excretion of unaltered quinidine amounts to 5 to 20 per cent of the administered dose.[64, 112] Various metabolic products are recovered from urine but account for less than 5 per cent of the quinidine administered.[112, 115] In view of the essentially complete absorption, limited localization and limited excretion, it is apparent that the fate of quinidine in the body is primariiy one of metabolic alteration.

Action on the Cardiovascular System in Animals

The main myocardial effects of quinidine are an increase in refractory period, thereby decreasing myocardial excitability, and a decrease in the rate of impulse conduction.[116, 117] Numerous observations have been made[118-124] of the action of the drug on the cardiovascular system of various animals. Comparison is difficult, however, not only because of species difference but also because of different anesthetics and operative procedures and, above all, different doses of quinidine given intravenously at varying rates.

Recent studies in dogs[125] have described the cardiovascular changes as plasma quinidine levels are progressively raised by continuous intravenous infusions of the drug. The changes observed are closely correlated with the plasma concentration of quinidine. A fall in arterial blood pressure occurs with low plasma levels. As the concentration rises, sinus slowing appears and progresses and is accompanied by various electrocardiographic manifestations of interference with impulse formation in the sinoauricular node. There is finally a transition to auriculoventricular-node rhythm, followed by intraventricular conduction block, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and death. These experimental observations cannot be applied directly to man. However, as discussed below, many of these cardiovascular effects seen in the dog may well have clinical counterparts.

Action on the Cardiovascular System in Man

Measurement of cardiac action and its relation to plasma concentration. The end of an arrhythmia is an all-or-none phenomenon that cannot be measured, and other indexes must therefore be used to determine the action of quinidine on the heart. Changes in rate or in the electrocardiogram permit determination of the time factors in the action of the drug and, in a few cases, enable the intensity of action to be related to the size of the dose. Pertinent observations have been recorded on:

The occurrence and degree of slowing of the auricular oscillations in the electrocardiograms of patients with auricular fibrillation[54, 113, 126-133] and auricular flutter.[7, 133, 134]

The occurrence and degree of prolongation of the QRS[135, 136] and QT[137] intervals of the electrocardiogram.

The effect on constant extrasystolic arrhythmias.[138, 139]

The slowing of the rate without restoration of normal sinus rhythm in patients with paroxysmal ventricular tachycardia.[46, 140, 141]

The occurrence and degree of increase in the ventricular rate in undigitalized patients with auricular fibrillation.[126]

The slowing of the rate without restoration of normal sinus rhythm in certain patients with paroxysmal auricular tachycardia.[142]

The disappearance of the electrocardiographic abnormalities in the Wolff–Parkinson–White syndrome (short PR interval and wide QRS interval).[143]

The development of bundle-branch block[144] in certain subjects with sinus tachycardia.

These studies following *oral* and *intramuscular* quinidine show that the time of onset of drug action, the time of maximum effect and the duration of action parallel closely changes in plasma concentration of quinidine described above.

Although plasma concentrations following *intravenous* quinidine are not known, the maximum cardiac effect as measured by auricular slowing in patients with auricular fibrillation and auricular flutter[7] occurs almost immediately after completion of the intravenous injection and certainly within ten minutes. The maximum effect of 0.4 gm. intravenously was approximately equivalent to 0.8 gm. by mouth. These and other observations[145] indicate that the duration of action after intravenous administration is only a few hours.

It has been suggested[113, 132] that the relation between plasma concentration and cardiac action of quinidine is not strictly quantitative. However, the correlation is good and it seems valid, therefore, to use changes in the plasma concentration as a guide to changes in the intensity of action on the heart.[107]

Little information is available, as yet, on the relation between the plasma concentration of quinidine and the prevention or treatment of various arrhythmias. In 2 patients[110] with recurrent auriculoventricular-node tachycardia, attacks were absent at plasma quinidine concentrations above 1.0 mg. per liter but recurred when the levels were lower. The dose required to maintain this "critical" level was at least 0.2 gm. of quinidine sulfate every four hours. In a small number of patients with various arrhythmias, restoration of normal sinus rhythm has occurred at levels ranging from 2 to 10 mg. per liter.[146]

Comparison of the cardiac action of quinidine and other cinchona alkaloids. The action of quinidine from natural sources has been compared with that of other natural and synthetic cinchona alkaloids.[126, 128-130, 137, 147-149]

These various studies indicate that, with equal doses, natural and synthetic quinidine show the same activity and dihydroquinidine is more active; cinchonidine, cinchonine and quinine are less active. Inasmuch as quinine is occasionally used instead of quinidine in the treatment of cardiac arrhythmias, it is of practical importance to appreciate the quantitative difference in the action of the two drugs. In addition to the greater activity of quinidine on the basis of equal doses, it has been found that the maximum effect on the rate of the auricular oscillations in auricular fibrillation obtainable with increasing doses of quinine is never as great as that obtainable with increasing doses of quinidine.[147] Accordingly, the two drugs are not completely interchangeable. However, quinine has been used effectively in the treatment of paroxysmal auricular tachycardia,[150, 151] paroxysmal auricular fibrillation,[151] paroxysmal auricular flutter[151] and paroxysmal ventricular tachycardia.[46]

Other cardiovascular effects. Various other cardiovascular effects of quinidine have been measured both in normal persons[137, 152] and in patients with cardiac disease,[152, 153] but the results are conflicting. After large single doses of quinidine sulfate by mouth, the heart rate has been found to show no significant changes[137, 152] or an increase[153]; arterial blood pressure has been observed to fall[152] or to remain unchanged[153]; cardiac output has shown no change in normal persons,[152] a decrease or no change in cardiac patients without congestive failure[152] and a rise from a previously low value in patients with cardiac decompensation.[152] These last patients also showed a fall in arterial pressure and drop in a previously elevated right ventricular pressure. A fall in arterial pressure and a drop in peripheral resistance without change in cardiac output has been attributed to an action of quinidine on the peripheral vascular bed.[152] The reported efficacy of quinidine in the treatment of angina pectoris[154, 155] suggests that the drug also causes dilatation of the coronary arteries.

Toxicity

Uncertainty about the toxicity of quinidine undoubtedly contributes to its limited use by many physicians. Although many questions regarding quinidine toxicity cannot be answered without further study, our experience and that of other clinicians indicate that serious side reactions are rare.[137, 156, 157]

Quinidine, like quinine, has been labeled "a general protoplasmic poison."[76] The term is meaningless, however, and the toxicity of these substances for vertebrates is low.[158]

*Cinchonism and other reactions.** In man, the most frequent side reactions are grouped under the term "cinchonism," the nature and severity of the symptoms varying, in general, with the size of the dose. In its mild form, this syndrome is not uncommon and includes nausea, abdominal discomfort, diarrhea, ringing in the ears and dizziness. If administration is interrupted, the symptoms usually subside promptly. On readministration, especially if the dose is increased more slowly,[54, 159] larger amounts may be given and higher plasma levels reached in the same patient without recurrence of symptoms. The little information available[54] suggests a lack of correlation between plasma concentration and the early symptoms of cinchonism. From 2.0 to 3.0 gm. of quinidine sulfate has been administered repeatedly by mouth with the development of only minor side effects.[160, 161]

Certain persons may develop mild cinchonism even after a small oral dose of 0.2 gm. This mild, not uncommon but unimportant reaction may be inconstant in the same subject on different occasions and is no contraindication to further administration of quinidine.

Rarely, syncope,[159] convulsions,[159] sudden collapse[162] and respiratory difficulty[163, 164] have been observed after a single small dose of quinidine. The evidence relating these phenomena to the administered quinidine is, however, inconclusive.

Reactions of an "allergic" nature have been described with quinidine but are rare. Skin rashes have been reported,[137, 165] but the best documented case reports concern the occurrence of fever[166] and thrombocytopenic purpura.[167] In each case the sensitivity has been *an acquired one, developing after one to three weeks of drug administration.* After the subsidence of the initial episode, readministration of a single small dose of quinidine has been followed by reappearance of the phenomena within two hours. In such cases quinine may be of value instead of quinidine, since persons sensitive to one are generally not sensitive to the other.[166, 168-173]

It has usually been recommended that, to detect sensitive persons, a small "test dose" of quinidine

*We have purposely avoided the term "idiosyncrasy." The literature on quinidine is needlessly confused by its use. *Webster's New International Dictionary of the English Language* defines "idiosyncrasy" as "a characteristic distinguishing an individual," and it may, therefore, properly be applied to many of these reactions.

be given. Inasmuch as reactions to quinidine may be expected to occur within a few hours after a dose, a longer period of observation is not necessary. The appearance of severe untoward symptoms following the first of a proposed series of doses will serve as indication for modifying the dosage schedule. It is pertinent to emphasize the infrequency of serious reactions to quinidine.

Cardiac toxicity. Although the potentially more serious toxicity of quinidine is related to its action on the heart, experience suggests that such toxicity is uncommon. The controversial problem of embolization in patients with chronic auricular fibrillation receiving quinidine will not be discussed here.[67] As mentioned above, increasing quinidine concentrations in dogs are associated with various manifestations of interference with normal cardiac impulse formation and conduction and, finally, with death. Although in some cases the relation to the drug is not definite, clinical counterparts of these experimental observations have been described in patients with various arrhythmias receiving quinidine. These include sinus arrhythmias,[67] auricular standstill,[174, 175] auriculoventricular block,[126] bundle-branch block,[144] ventricular extrasystoles,[54, 126, 162, 176, 177] ventricular tachycardia,[54, 65, 126, 162, 176] transient ventricular fibrillation[178-181] and death.[7, 54, 182, 183] In most cases these phenomena have been observed with moderate or large doses of quinidine. However, sufficient information is not available to indicate the likelihood of producing an untoward cardiac reaction in a given patient with a particular dose or plasma level of quinidine.

When quinidine is being administered, particularly in large doses, it is important to have some guide that will warn of approaching cardiac toxicity. It has been suggested that QRS lengthening of more than 25 per cent of the control value is not safe,[136] but more marked prolongation of the QRS complex has been witnessed without untoward effect when the situation required larger amounts of the drug.[184] When quinidine administration is associated with auricular standstill, bundle-branch block, a rise in ventricular rate, ventricular extrasystoles, ventricular tachycardia or transient ventricular fibrillation the drug should be stopped. Frequent electrocardiograms are thus helpful in controlling the therapeutic administration of quinidine, and correlation of electrocardiographic changes and plasma concentrations now being carried out[185] should give information of considerable value.

Contraindications

The only absolute contraindication to the administration of quinidine is a history of serious reaction to the drug.

Relative contraindications frequently mentioned include long-standing auricular fibrillation, bundle-branch block, auriculoventricular block, severe cardiac failure, marked cardiac enlargement, long-standing valvular disease, subacute bacterial endocarditis, various acute infections and advanced age of the patient. The evidence that these factors increase the likelihood of cardiac toxicity is not conclusive, and they should not prevent use of the drug when there is a definite indication. Acute myocardial infarction has been considered both an indication and a contraindication. In such cases clinical experience with prophylactic doses of 0.2 to 0.3 gm. of quinidine sulfate three or four times a day has not revealed any unusual incidence of toxic reactions.

Indications

Quinidine may be used effectively in the prevention and treatment of paroxysmal auricular fibrillation, paroxysmal auricular flutter, paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia and ventricular extrasystoles. It has also been found to be of value in the treatment of certain cases of chronic auricular fibrillation when the arrhythmia may be causing recurrent embolization[186] or cardiac failure.[187]

Quinidine is generally recognized as the drug of choice in paroxysmal ventricular tachycardia. In most other arrhythmias, however, other agents (Table 1) may be effective, and the relative value of quinidine cannot be accurately determined on the basis of the available evidence.

Preparations and Routes of Administration

Since it is promptly and almost completely absorbed from the gastrointestinal tract, quinidine is generally administered by mouth. Quinidine sulfate (*U.S.P.*) is available in 0.2-gm. and 0.3-gm. tablets for oral use.

Parenteral administration may be necessary when an acute arrhythmia is associated with collapse, unconsciousness, vomiting or other factors that make oral use impossible or absorption from the gastrointestinal tract uncertain. Injectable quinidine preparations are not readily available but may easily be prepared as stable aqueous solutions that can be stored in ampoules for emergency use. A 15 per cent solution of quinidine hydrochloride dissolved with the addition of 15 per cent antipyrine and 20 per cent urea[156] and a 15 per cent solution of quinidine lactate[188] have been used in man — the first intramuscularly, and the second both intramuscularly and intravenously. Quinidine acts more quickly intramuscularly than by the oral route, is at least as effective and may cause even fewer side reactions.[156] Quinidine has been used intravenously for therapeutic purposes,[28, 189-193] but the advantage of the greatly increased speed of action is rarely important enough to warrant the greater danger of serious toxicity. The intramuscular route is the one of choice for parenteral administration.

Dosage Schedules

Schedules of quinidine administration for prophylactic and therapeutic purposes differ considerably and must be established in accordance with the requirements of a particular case.

Prophylactic administration. In many patients with recurrent paroxysms, attacks are so infrequent and mild that continued administration of quinidine is not warranted. Prophylactic administration is instituted only when paroxysms of tachycardia tend to recur frequently or when single paroxysms are serious because of their severity or their nature (for example, ventricular tachycardia). In such patients individualization of dosage is important; initial doses of 0.2 gm. three times a day, if inadequate to prevent recurrence of the paroxysms, may be followed by larger doses and more frequent administration; 1.0-gm. doses have been given repeatedly for long periods.[54] In certain persons it may be necessary to arrange the doses to minimize the interval between the last night and the first morning dose. In these cases enteric-coated tablets may be of value. Because of the rapidity with which quinidine is eliminated, long-continued administration carries no danger of cumulative toxicity, and the drug has been administered regularly for years without ill effect.[54, 135]

Quinidine is often used to prevent the occurrence of arrhythmias, which may develop during acute myocardial infarction and thoracic surgery. In patients with acute myocardial infarction 0.2 to 0.3 gm. is customarily administered three or four times during the day. In view of the unpredictability of the occurrence of these arrhythmias, the efficacy of such prophylaxis is difficult to evaluate. When necessary, the size of the individual dose can be increased to 0.4 or 0.6 gm.

In patients undergoing thoracic surgery, quinidine is often used prophylactically during the operation and the early postoperative period. A dose of 0.4 to 0.6 gm. is administered by mouth or intramuscularly one or two hours before the operation and continued every six to eight hours for a few days postoperatively.

Therapeutic administration. In the treatment of an acute arrhythmia the urgency of the situation will influence considerably the manner in which quinidine is administered. Effective therapeutic results can be achieved with oral administration, but when necessary the drug may be given intramuscularly. In most cases, with oral or intramuscular routes, doses are repeated at intervals of about two hours. This permits observation of the maximum beneficial and untoward effect of each dose. When a more rapidly increasing effect is required, the drug may be given every hour.

An initial dose of 0.2 to 0.6 gm. is commonly used, the larger amount being given in the more urgent situation. A favorable response is manifested by definite cardiac slowing, rise in blood pressure, decrease in symptoms or improvement in the patient's general condition. If this occurs after the first dose, the same dose may be repeated every two hours as long as improvement continues. Usually, if normal sinus rhythm has not returned after three or four such doses, the size of the dose is increased by 0.1 or 0.2 gm. This dose may then be given three or four times before it is increased further.

If a favorable response is not seen after the first dose, the second dose should be 0.1 or 0.2 gm. larger than the first, and subsequent doses may similarly be increased. In most cases individual doses do not often need to be raised above 1.2 gm. before normal rhythm is restored.

In the treatment of chronic auricular fibrillation many different dosage schedules have been recommended. As utilized by us, the drug is administered every four hours, and the size of the individual dose increased by 0.2 gm. every twelve to twenty-four hours. Ample time is therefore afforded to observe the effect of a particular level of quinidine. In the past, the drug has too often been declared ineffective in this disorder after inadequate trial because arbitrary fixed schedules have been followed.

Summary

Physiologic and pharmacologic data accumulated in the past few years, although providing a more rational basis for the use of quinidine, are as yet incomplete. Quinidine is of outstanding value in the management of paroxysmal ventricular tachycardia; its relative efficacy in other paroxysmal arrhythmias has not been established.

Miscellaneous Measures

Grouped in this section are other drugs that have been used in the prevention and treatment of cardiac arrhythmias. Several — for example, procaine, quinacrine and Metrazol — are of value for other clinical conditions, and others — such as morphine, Paredrine and Neo-Synephrine — are useful in the treatment of certain effects consequent to a rapid heart rate, such as pain, restlessness, hypotension and peripheral vascular collapse. These drugs are listed in Table 1. Further studies of these drugs may lead to better treatment of cardiac arrhythmias. It is likely that some drugs on the list have been unjustifiably credited with prophylactic or therapeutic value. The establishment of rational methods for using older agents in these disorders may be as important as, if not more important than, the development of new ones. As pointed out above in the first two sections of this review, the multiplicity of measures used in cardiac arrhythmias has resulted in inadequate study of most of them.

The various surgical procedures that have been carried out on the sympathetic nervous system (Table 1) have had a very limited use, generally for

prophylactic purposes, in patients whose repeated paroxysms of tachycardia have not been prevented by medical measures.

Digitalis Glycosides

The main indication for the use of cardiac glycosides is congestive heart failure regardless of the rhythm. Digitalis preparations are widely used in patients with paroxysmal supraventricular tachycardia, auricular fibrillation and auricular flutter particularly if heart disease is present and the paroxysmal nature of the tachycardia is not clear. The mechanism of action of digitalis in preventing and stopping auricular arrhythmias is obscure. It is important to remember that paroxysmal tachycardia of ventricular origin is considered by many to represent a contraindication to digitalis therapy.

Choice of preparation. The various considerations governing the selection of a digitalis glycoside have been the subject of a recent report.[194] Numerous digitalis preparations have been used intravenously in the treatment of acute supraventricular arrhythmias. Although a great deal of emphasis has been placed on lanatoside C intravenously,[59, 195, 196] there is no clear evidence that it accomplishes more than other digitalis preparations such as Digalen,[59] Digifolin[6, 7] and ouabain.[197] Oral preparations have been used to prevent the recurrence of these arrhythmias.[198]

Side effects. The evidences of digitalis overdosage are well known. In the various studies with intravenous lanatoside C mentioned above, only occasional nausea and rare transient ventricular extrasystoles have been observed.

Efficacy in treatment of paroxysmal supraventricular arrhythmias. Rapid restoration of normal rhythm has been observed after half to full "digitalizing" doses of cardiac glycosides intravenously in patients with paroxysmal auricular tachycardia, paroxysmal auricular fibrillation and paroxysmal auricular flutter. In many cases the effect occurred within five to ten minutes of the injection. In others, the change in rhythm occurred after a longer interval, up to twenty-four hours, and the relation to the drug was therefore not definite. In some cases ventricular slowing may be noted, although normal sinus rhythm is not restored. This may result in symptomatic improvement, and unless electrocardiograms are taken, sinus rhythm may be thought to have returned.

In several cases of paroxysmal auricular tachycardia, Weisberger and Feil[59] found that carotid-sinus pressure, although previously ineffective, stopped the attack immediately when applied after the administration of lanatoside C. This is in accord with the observation that digitalis increases the sensitivity of the carotid-sinus reflex.[40, 60] A similar effect has been seen, as pointed out above in the first section, after acetyl-beta-methyl-choline and neostigmine.

Efficacy in preventing paroxysmal supraventricular arrhythmias. Tandowsky[198] has maintained digitalization with 0.5 to 1.0 mg. of lanatoside C by mouth daily in 8 patients with paroxysmal auricular flutter and auricular tachycardia. Only three attacks occurred during a fifteen-month period of treatment, compared to twenty-four during a twelve-month period prior to digitalization. Although the observations were not completed by the omission of digitalis to determine if the frequency of attacks increased, the results are consistent with our own experience.

Summary. Digitalis preparations are of value in the prevention and treatment of paroxysmal supraventricular arrhythmias. The intravenous route of administration has been found particularly useful in stopping paroxysms of tachycardia. These substances can be given safely in therapeutic doses, may be expected to be effective in many patients and may, of course, be of value for associated cardiac failure.

Magnesium Sulfate

High concentrations of magnesium ion depress the cardiac conduction system and heart muscle. As the serum concentration of magnesium ion is increased in animals, prolongation of the PR and QRS intervals is observed; the cardiac rate decreases and cardiac arrest occurs.[199, 200] Stanbury[201] has shown that the magnesium ion has a blocking action on sympathetic ganglions; the cardiac slowing may therefore be related to this effect as well as to direct cardiac depression. In dogs magnesium sulfate has been found to be of some value in preventing ventricular arrhythmias due to mercurial diuretics.[202]

Although magnesium sulfate has been found to be of value in various types of paroxysmal tachycardia,[203-207] similar doses have little effect on the normally beating human heart.[203, 208]

Method of administration. Intravenous doses range from 10 to 20 cc. of a 10 to 30 per cent (in most cases, 20 to 25 per cent) solution of magnesium sulfate in distilled water.

It appears that the concentration of the drug reaching the heart is the important factor; accordingly, intravenous injection is accomplished in twenty to thirty seconds. If there is any effect on the arrhythmia, it occurs at once.

Side effects and contraindications. An unpleasant though transient generalized feeling of intense heat and an associated drop in blood pressure (20 to 30 systolic) may occur[204, 206] immediately after the intravenous administration of magnesium sulfate. There may also be perspiration, flushing, dizziness, frequently nausea but rarely vomiting and a transient feeling of generalized weakness. Ventricular premature beats may be observed for a short period.[206] It has been suggested[206] that magnesium sulfate should not be used in the presence of marked myocardial damage, intraventricular-conduction de-

fects or gallop rhythm. Since magnesium is excreted largely by the kidneys,[76] it should be used with care in the presence of renal failure.[203]

Efficacy in treatment of various arrhythmias. Beneficial action has been reported[203-207] in paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia and ventricular premature beats due to digitalis. The effect, especially in the digitalis-induced extrasystoles, has sometimes been only transient. Increase in auriculoventricular block has been seen in auricular flutter but, in general, no beneficial effect has been observed in this arrhythmia or in auricular fibrillation.

Summary. Magnesium sulfate has been less widely used in the management of paroxysmal tachycardias than the digitalis glycosides and other agents. Its short duration of action makes its prophylactic use impractical. Therapeutically, it appears to be effective in many cases, but its use is associated with transient unpleasant side effects.

Summary of Therapeutic Programs in the Arrhythmias

The large number of available measures for the management of paroxysmal arrhythmias poses a considerable problem for the physician. It is pertinent, therefore, that we summarize our own programs in the various arrhythmias.

Paroxysmal Supraventricular Tachycardia

Carotid-sinus and eyeball pressure are simple, safe means of reflex vagal stimulation, effective often enough to warrant their trial as the initial procedures in all cases. These measures, particularly carotid-sinus stimulation, should be repeated frequently along with some of the miscellaneous measures discussed above.

If these simple measures fail, sedation (by barbiturates) and rest are often associated with restoration of normal rhythm. In the absence of pulmonary congestion, angina pectoris, congestive failure, vascular collapse, cerebral manifestations or embolism this nonspecific therapy may be continued for twenty-four to forty-eight hours or longer before other measures are used. Neostigmine, Neo-Synephrine, Paredrine or acetylcholine may then be administered, particularly in young persons with normal hearts. If parasympathomimetic drugs are used (such as Neostigmine) reflex vagal stimulation should be repeated. Although previously ineffective, carotid-sinus stimulation a few minutes after administration of these drugs often stops an attack. Although ipecac is unpleasant because of the necessary association of vomiting with its beneficial action, it is safe, and we have used it successfully. In the patient with cardiac disease, especially if congestive failure is present and the simple reflex measures mentioned above have failed, digitalis is the drug of choice. Quinidine is of value in many cases refractory to these measures.

If the tachycardia persists, other agents reported to be of value, such as magnesium sulfate, potassium salts, procaine and quinacrine may be tried.

Paroxysmal Auricular Fibrillation and Paroxysmal Auricular Flutter

It should be emphasized that in most cases sedation and rest alone may be accompanied by reversion to normal sinus rhythm. If not, and in the presence of symptoms, the choice of therapy lies between quinidine and digitalis. In young persons without heart disease we use quinidine. In the presence of heart disease or congestive failure, or both, digitalis is the drug of choice.

Chronic Auricular Fibrillation

When treatment is necessary, digitalis is used. In some unusual cases of congestive failure or embolism due to arrhythmia, quinidine has been used successfully.

Ventricular Extrasystoles

The avoidance of tobacco and coffee and the use of sedatives are very often beneficial. If not, quinidine, in doses outlined above, may be used effectively.

Paroxysmal Ventricular Tachycardia

Quinidine is the drug of choice if specific treatment is necessary. The dosage schedules have been given above. In refractory cases, other drugs, such as magnesium sulfate, potassium salts, diethylaminoethanol and morphine, may be tried.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35421

PRESENTATION OF CASE

A five-month-old-male infant was admitted to the hospital because of diarrhea.

The patient was born prematurely of a pregnancy that was complicated by kidney disease diagnosed as pyelitis. However, the baby's development had been entirely normal, and three siblings were living and well. A week before admission he began to have diarrhea that did not respond to limitation of solid foods, passing about eight liquid stools a day, which were yellow at first and later green. Two days before admission a physician prescribed a mixture of triple sulfonamides, bismuth and paregoric of which an unknown amount was taken over the next twenty-four hours. On the following day the fluid intake was only 5 ounces, and the mother noted that the baby's urine was pink. On the day of admission the baby was seen at another hospital where physical examination showed a drowsy, dehydrated infant with a temperature of 103°F. and a pink diaper stain. There was edema of the penis and scrotum and a mild pharyngitis. The urine was packed with red cells and contained 90 mg. per 100 cc. of albumin. The hemoglobin was 8.7 gm. per cent, the red-cell count 2,700,000, and the white-cell count 11,500, with 66 lymphocytes, 32 per cent mature neutrophils, 1 per cent stab cells, and 1 per cent basophils. The blood was type O and Rh+. The nonprotein nitrogen was reported as 377 mg. per 100 cc.; the sulfonamide level was 1.4 mg. per 100 cc. He was given a 180-cc. infusion of 5 per cent glucose in physiologic saline solution, 80 cc. of whole blood and 300,000 units of procaine penicillin, and referred to this hospital.

On admission the baby was pale, comatose and gasping. The eyes were turned up, and there were convulsive movements of the right arm. Coarse bubbling rales were heard bilaterally. The heart rate was 140 without murmurs. The systolic blood pressure was thought to be 140 by one observer. A blood culture was later reported as negative.

Oxygen and artificial respiration were begun immediately, and after some thirty minutes the baby improved. However a second left-sided convulsion followed, subsiding without treatment. He was then given 0.16 mg. of Cedilanid intravenously and 15 mg. of phenobarbital subcutaneously. At this point a third convulsion occurred, and the baby stopped breathing.

In spite of artificial respiration, oxygen, caffeine and sodium benzoate intravenously and 0.5 cc. of epinephrine injected into the heart, the infant died two hours after admission to the hospital.

Differential Diagnosis

Dr. John Crawford: The important facts seem to be the following: this five-month-old infant was entirely well until seven days before death. For one week he had had diarrhea amounting to eight stools daily, which were liquid and yellow at first, becoming green but without blood.

In the infant under one year of age diarrhea is a frequent symptom of extra-enteral infection. Nowadays, with milk pasteurization and good refrigeration, diarrhea due to true enteral infection is becoming less and less common. I think we may guess that the child had a parenteral infection, probably an upper respiratory infection, with diarrhea as the chief symptom.

Apparently, this mother of three children had had previous experience with infantile diarrhea and immediately began limitation of solid food. When this failed to alleviate the difficulty the family physician was called. We are not told what he found. My guess is that he found evidence of a pharyngitis or otitis media, for which he prescribed sulfonamides. He also prescribed bismuth and paregoric, which sometimes are effective in quieting a mild diarrhea but rarely in severe diarrhea.

On the day before death the infant began to refuse fluids, and it was said that his urine was pink, this, from subsequent findings, apparently being due to blood. His condition rapidly deteriorated, for the next day he was taken to a hospital, where he was found to be in a critical condition.

The physical examination at that hospital showed a drowsy, dehydrated infant, with a temperature of 103°F. and an upper respiratory infection. Edema of the penis and scrotum was noted, without edema elsewhere. The urine was grossly bloody. Evidently no casts were seen. We are told that the urine contained 90 mg. of albumin per 100 cc. This is not a great deal: the commonly used heat and acetic acid test would be interpreted as + to ++ with this degree of albuminuria. We do not know whether the urine was concentrated or dilute.

A considerable anemia was present. The prematurely born infant of five months ordinarily has about 10 gm. of hemoglobin. This infant had 8.7 gm. I would interpret this figure to represent a marked deviation from normal in view of the clinical dehydration. Serum chemical analyses revealed a nonprotein nitrogen of 377 mg. per 100 cc., a startlingly high figure; the blood sulfonamide level was only 1.4 mg. per 100 cc.

In short, the infant was obviously critically ill. He was given emergency treatment consisting of blood to correct the anemia, fluid to combat dehydration and penicillin for infection, and was then referred with all dispatch to this hospital.

Following arrival here, we learn little more to help in making the diagnosis before death. The child was in collapse; he had episodes of convulsive movements. One observer thought that he had hypertension. He died only two hours after admission.

There are several diagnoses to be considered. The older texts say that syphilitic nephritis is the commonest hemorrhagic nephritis in infants under one year of age. In this part of the country congenital syphilis is seen with ever-diminishing frequency. I would expect the protocol to mention syphilis in the mother or a positive blood test in the child if this merited further consideration.

A sulfonamide tubular nephrosis due to crystal formation might be considered, but there are several points against this diagnosis. The physician treating the infant wisely used a mixture of three sulfonamide drugs so that the antibacterial effect would be proportional to the sum of the serum concentrations of each, and yet the danger of renal precipitation in the face of diarrhea would be minimal since the solubility of each sulfonamide component is independent of the other two in the renal tubular fluid. Furthermore, the blood sulfonamide level of 1.4 mg. per 100 cc., obtained twenty-four hours or less after the last dose in an oliguric patient, is indicative of conservative use of the drug.

The child might have had a sulfonamide-sensitivity nephritis. This would be unexpected so soon after the initial dose. We have no history of prior sulfonamide administration, which might account for an accelerated reaction.

Acute hemorrhagic nephritis is a definite possibility. We have evidence of a preceding respiratory infection, which might well have been streptococcal. We have hematuria, oliguria, nitrogen retention and possibly hypertension with encephalopathy.

To make this diagnosis I should like to have the report of granular casts in a concentrated urine. Such an extremely high nonprotein nitrogen is unusual. There was less albuminuria than I would expect. Moreover the disease itself, while very common in childhood, is distinctly rare in the infant under six months. I cannot rule out acute hemorrhagic nephritis, but I do not believe that it fits the clinical picture as well as another diagnosis.

Although a transfusion nephrosis seems unlikely, since the symptoms were well established before the giving of blood, it might be mentioned that there is some evidence that transfusion of blood in which the plasma complement titer is high may aggravate an already existing glomerulonephritis.

The diagnosis I favor here is that of "hemorrhagic infarction of the kidney." Quite a large number of cases have been reported in infancy, particularly as a complication of diarrheal episodes. Barenberg[1] and Hepler[2] have reported a considerable number of cases in infancy.

I would suppose that the sequence of events in this infant was as follows: seven days before death

he had contracted an upper respiratory infection that resulted in moderate diarrhea. The day before entry, possibly as a result of factors such as dehydration and diminished blood volume, thromboses began to form in the small vessels of the kidneys, with resultant hematuria and oliguria. This process, once initiated, extended very rapidly and may have involved not only the blood vessels of the kidney but also those of the pelvis, giving rise to the peculiar edema of the penis and scrotum observed on physical examination. The extravasation of blood into the infarcted renal tissues resulted in the marked anemia and contributed to the extreme elevation of the nonprotein nitrogen. When this condition is bilateral or goes unrecognized for any length of time, collapse and death soon result.

Campbell and Matthews[3] emphasize that the diagnosis should be made clinically on the basis of the history and on the physical finding of firm flank masses. However, Barenberg,[1] describing 5 cases in infants, was unable to palpate a swollen kidney in any of them.

In summary, then, the protocol suggests to me either acute hemorrhagic nephritis following a streptococcal respiratory infection or so-called "acute hemorrhagic infarction" of the kidney. Of these two diagnoses, the latter seems to fit the few facts outlined in the protocol somewhat better than the former.

Clinical Diagnosis

Acute hemorrhagic nephritis.

Dr. Crawford's Diagnoses

Diarrhea due to acute pharyngitis.
Dehydration secondary to diarrhea.
Acute hemorrhagic infarction of kidneys.

Anatomical Diagnoses

Ischemic necrosis of kidneys.
Pulmonary edema.
Petechial hemorrhages in brain.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Crawford's prediction is, I think, essentially correct. The only major lesion at autopsy was found in the kidneys, which were markedly enlarged and grossly hemorrhagic. Microscopical examination showed a picture, which to me is unfamiliar in infancy, of extensive necrosis, predominantly in the cortex, though some foci were present in the pyramids. This necrosis was most marked in the tubules and was present to a less degree in the glomeruli. We could find no thrombosed vessels anywhere in the kidneys. There were a few small areas in which complete infarct-like necrosis with interstitial hemorrhage was present. The majority of the kidney showed a much less severe, degenerative process from which one would, I think, assume that recovery might have been possible. The major part of the blo evident on gross examination lay in the lumen the tubules, giving evidence that there had be massive leakage of blood through the glomeru tufts, and, quite often, Bowman's capsule was fou acutely distended with red cells.

Other parts of the body showed what I thi were only secondary features: extensive pulmona atelectasis and edema and multiple, minute petech hemorrhages throughout the brain — a not too u common complication of uremia.

Dr. Alfred Kranes: How does the picture diff from bilateral cortical necrosis?

Dr. Mallory: It is very similar, and that is, i fact, the diagnosis that I made.

Dr. Kranes: Does that occur in infants?

Dr. Mallory: Dr. Crawford knows more abou that than I do, and I would like to ask him.

Dr. Crawford: I tried to emphasize that. I pu "acute hemorrhagic infarction" in quotation mark because I did not think it was a good descriptive term. In the pediatric literature "acute hemorrhagi infarction" is used to describe a condition that seem to be very similar to the "acute cortical necrosis" of the adult literature. The terms probably refer to the same disease.

Dr. Mallory: I think there is very little doub that it is the same condition. My only hesitancy in calling it acute cortical necrosis was the fact tha there was some involvement of the pyramids which is unusual, at least in the adult cases of cortical necrosis. Cortical necrosis is seen most commonly in pregnancy, but it can occur in other conditions, and in the male as well as the female. It has been seen in association with a variety of infections and occasionally follows shock and burns. Vascular thrombosis may or may not be present and may well be secondary rather than primary. I suspect that this is also true of the lesion described as "renal thrombosis with infarction" in the pediatric literature.

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CASE 35422

Presentation of Case

First admission. A fifty-five-year-old Greek barber was admitted to the hospital because of swelling of the legs, genitalia and abdomen.

The patient was well until some eight years before admission, when he first began to notice evening ankle edema, which subsided on rest at night. This persisted until about two months before entry, when the swelling became progressively worse and no longer cleared by morning. This was followed

soon afterward by swelling of the genitalia and, to a lesser extent, the abdomen. During the month before admission he had experienced a sense of discomfort in both upper quadrants, with sharp pain on deep breathing. He also noticed a three-flight exertional dyspnea without orthopnea. There was no history of nausea or vomiting, hematemesis, melena or recent jaundice. His appetite was good, but he had lost about 15 pounds in weight during the last eighteen months. The patient gave a history of painless jaundice some twenty-five years before. He stated that he drank two or three glasses of wine a day. One week before admission the patient was seen in the Outpatient Clinic, where diuretics were administered with marked diminution of swelling.

The patient had a penile lesion twenty years before and was treated with thirty intravenous injections.

Physical examination revealed a well developed and well nourished man in no acute distress. There was slight icterus of the skin and scleras but no spider angiomas. The chest was clear except for a few rales in the right base. The liver edge was palpated two or three fingerbreadths below the right costal margin, and the spleen two fingerbreadths below the left costal margin. There were many prominent veins over the abdomen and shifting dullness without a fluid wave. Tenderness was present in both upper quadrants. There were several external hemorrhoidal tabs, and the prostate was slightly enlarged. The lower legs showed a ++ edema, varicosities and pigmentation of the skin.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 95 systolic, 60 diastolic.

The urine was yellow and cloudy and had a specific gravity of 1.012. It gave a +++ test for albumin but contained no bile. There were 20 to 30 white cells per high-power field in the sediment. A urine smear showed rare clusters of gram-positive cocci and a urine culture grew *Staphylococcus albus*. The blood hemoglobin was 10 gm., and the white-cell count 3800, with 56 per cent neutrophils. The blood nonprotein nitrogen was 40 mg., and the total protein 7.11 gm. per 100 cc., with an albumin of 3.55 gm. and a globulin of 3.56 gm. The fasting blood sugar was 124 mg. per 100 cc., and the cephalin flocculation test was ++ and ++++ in twenty-four and forty-eight hours; the thymol turbidity was 13.5 units, the cholesterol 241 mg. and cholesterol esters 115 mg. per 100 cc. The prothrombin time was 15 seconds (normal, 15 seconds). The serum van den Bergh reaction was 0.6 mg. per 100 cc. direct and 0.8 mg. indirect, and the alkaline phosphatase 5.2 units per 100 cc. A bromsulfalein test showed 36 per cent retention of the dye. A blood Hinton test was positive.

A gastrointestinal series was negative. No varices were identified. The spleen was enlarged, and a roentgenogram of the chest showed only slight prominence of the left ventricle. A phenolsulfonephthalein test showed normal excretion, and a urea-clearance test gave specific gravities of 1.012, 1.015 and 1.015. The patient was advised concerning a high-calorie, high-protein, low-sodium diet and was discharged on the ninth hospital day somewhat improved. During this period in the hospital daily afternoon temperature rose to about 100°F. Four separate urine specimens showed 5 to 40 white cells per high-power field in the sediment and had specific gravities that ranged from 1.012 to 1.015. On two occasions the urine contained occasional granular and hyaline casts.

Final admission (approximately two months later). In the interval the patient noted progressive weakness and loss of appetite. One month before entry swelling of the legs, genitalia and abdomen again became marked despite diuretic therapy. An abdominal paracentesis was performed by a physician, with the removal of a considerable amount of fluid, but the abdominal swelling soon recurred. His skin became increasingly more jaundiced, and he had experienced nausea and vomiting during the three days before admission.

The findings on physical examination were essentially the same as those at the time of the previous admission, with the addition of pulsating neck veins.

The temperature was 99°F., pulse 80, and the respirations 20. The blood pressure was 136 systolic, 76 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ test for albumin and bile. The sediment contained 2 or 3 red cells and 6 to 8 white cells and many hyaline and granular casts per high-power field. The blood hemoglobin was 9.5 gm. and the white-cell count 6000, with 74 per cent neutrophils. The red cells showed moderate anisocytosis and hypochromia. The blood nonprotein nitrogen was 35 mg., and the total protein 7.85 gm. per 100 cc., with an albumin of 3.08 gm. and a globulin of 4.77 gm. The cephalin flocculation test was +++ and ++++ in twenty-four and forty-eight hours. The serum van den Bergh reaction was 6.0 mg. per 100 cc. direct and 8.4 mg. indirect, and the alkaline phosphatase was 5.4 units per 100 cc. The prothrombin time was 21 seconds (normal, 15 seconds).

The patient became increasingly more drowsy and icteric, ate little and vomited frequently. The edema did not respond to the usual therapy. On the eighth hospital day after being comatose for twenty-four hours, he died.

Differential Diagnosis

Dr. Jacob Lerman: I should like to know if mention is made of treatment for the urinary infection during the first admission.

DR. TRACY B. MALLORY: There is no notation about therapy for pyelitis.

DR. LERMAN: The initial symptoms could be explained either by right-sided heart failure or by the beginning of portal obstruction or portal cirrhosis. The slow development of edema, first in the legs and then in the abdomen, and finally the enlargement of the liver suggest the course of events that one sees in right-sided failure. However, he had no symptoms of right-sided failure. Mention is made of three-flight dyspnea. That is normal for all of us. There was no respiratory distress on examination. In spite of the type of onset, there was no evidence of cardiac involvement. He had an episode of painless jaundice, which does not seem to have much bearing on the problem. No doubt the intake of wine is of importance in this particular eastern Mediterranean race. He had evidence of acquired syphilis as indicated by a positive blood Hinton reaction; it may have played an important role.

On physical examination he had mild icterus, enlargement of the liver and spleen, fluid in the abdomen, prominent veins over the abdomen, hemorrhoids, varicosities and edema of the legs — all of which fit the diagnosis of portal cirrhosis. I cannot explain why he had such a low blood pressure. Undoubtedly he had a urinary infection. Evidence in the record indicates some degree of pyelonephritis. In addition, the abdominal pain, the anemia, the leukopenia, the reversed albumin-globulin ratio, the positive cephalin-flocculation test, the low cholesterol esters of 115 mg. per 100 cc. of a total of 241 mg., the bromsulfalein retention all speak for liver damage of the type one sees in portal cirrhosis. I assume that the fever was due to urinary infection, although fever is not uncommon in cirrhotic patients.

May we see the x-ray films?

DR. JAMES J. MCCORT: An examination of the gastrointestinal tract was made at the time of admission. The spot films of the esophagus show normal rugae without evidence of varices. The stomach shows no definite abnormality. There is a small diverticulum in the third portion of the duodenum. It is apparent that the spleen is enlarged and pressing on the stomach. There is also some enlargement of the left lobe of the liver as shown by the compression of the stomach.

The chest film taken on admission reveals clear lung fields. The heart is slightly prominent in the region of the left ventricle; there is no bulging anteriorly to indicate right-sided heart enlargement. It can be seen that the right leaf of the diaphragm is slightly higher than usual. A film of the chest at the time of the second admission, two months later, discloses an increase in vascular markings in both lung fields. The right leaf of the diaphragm is higher, and there is a small amount of fluid in the right costophrenic angle, posteriorly. A slight under-aeration of the right lower lobe may secondary to the high right leaf of the diaphra

DR. LERMAN: Can you judge whether or the left lobe of the liver is the larger portion?

DR. MCCORT: No, a film of the entire abdo was not obtained.

DR. LERMAN: The subsequent rapid downh course, in addition to the x-ray appearance of creased vascular congestion and the pulsating ne veins, again raises the question of congestive failu It may be just incidental to the major proble As I said before, all the facts so far seem to fav a diagnosis of ordinary portal cirrhosis.

We must consider other diagnoses such as syph litic cirrhosis or gumma of the liver. The additio evidence that the left lobe of the liver was lar is a characteristic finding in syphilitic cirrhos This is not sufficient evidence, however, to ma the diagnosis, but it is suggestive. On the oth hand, it is difficult to know whether syphilit cirrhosis is different from ordinary portal cirrhosi Many people believe that they are one and the sam thing. Gumma is somewhat different. A gumm usually appears in the left lobe. It is the onl suggestive bit of evidence. Hemochromatosis ma be mentioned because he had pigmentation of th leg, but he did not have pigmentation elsewher or evidence of diabetes. I assume that the pig mentation was due to stasis dermatitis associate with varicosities. Amyloid disease should be men tioned, even though there was no obvious caus for amyloidosis, other than possibly cirrhosis it self. The presence of a large liver and spleen an the albuminuria are consistent with a diagnosis o amyloidosis. Unfortunately, we have no othe evidence, such as a Congo-red test. We can only mention it. Even primary amyloidosis might be a possibility.

Hepatoma should be mentioned, particularly in view of the rapid downhill course following the initial admission. The description of the liver is certainly not suggestive of hepatoma. Yet, in the presence of cirrhosis of long standing, rapid downhill course and weight loss, there is a good possibility that he had hepatoma. This produced sufficient obstruction to the biliary radicles to cause rapid liver failure.

We should also discuss the cause of death. Obviously he died from cholemia. What are the possibilities? I have already mentioned the co-existence of hepatoma. In addition, a patient with cirrhosis is rather subject to episodes of hepatitis or degeneration of the liver. I have seen several patients with portal cirrhosis who suddenly developed acute or subacute yellow atrophy or some sort of change in the cells that may be labeled hepatitis. The course here would suggest that he developed some such process as subacute yellow atrophy.

I must conclude with a diagnosis of portal cirrhosis, probably hepatoma, and probably a super-

imposed subacute degenerative process, such as subacute yellow atrophy.

DR. ALFRED KRANES: When Dr. Lerman says "portal" does he mean of the so-called alcoholic type?

DR. LERMAN: Yes.

DR. KRANES: May not the previous history of jaundice have been a factor in the later development of cirrhosis? It is hard to tell from the history. One wonders if it was due to arsenic. Apparently he had syphilis twenty years previously and was treated with arsenic.

DR. LERMAN: One would expect the late damage from arsenic or hepatitis to develop within a few years, or there would be recurrent episodes of this damage as is so often observed following hepatitis — until it ends up in biliary cirrhosis.

CLINICAL DIAGNOSES

Cirrhosis of liver.
Infectious hepatitis.

DR. LERMAN'S DIAGNOSES

Portal cirrhosis.
Hepatoma — probable.
Subacute yellow atrophy — probable.

ANATOMICAL DIAGNOSES

Cirrhosis of liver, portal.
Hepatoma, with extension into vena cava and right auricle of heart, and pulmonary metastases.
Esophageal varices.
Thrombosis of portal vein.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The exterior surface of the liver showed the coarse granularity characteristic of a long-standing cirrhosis. The dome of the right lobe showed in addition a large nodule 6 cm. in diameter that projected upward 2 to 3 cm. from the surrounding tissue. When the liver was sectioned sagittally it was evident that the inferior vena cava was completely filled with a tumor thrombus that extended up into the right auricle of the heart. Tracing the tumor backward in sections of the liver, it was obvious that the hepatic veins were occluded, and there was a primary tumor in the liver substance occupying a considerable part of the right lobe. Histologically, it was a hepatoma, a primary liver-cell carcinoma, developing as it almost invariably does in a liver that has been cirrhotic for a long period. The cirrhosis itself was old and inactive. Beyond saying that it was a portal cirrhosis, I cannot classify it further. I cannot say whether or not it might have been a result of previous hepatitis or a result of alcoholism — greater than admitted. There was evidence of acute degeneration of liver cells in many parts of the organ itself, infarct-like in character and secondary to the numerous vascular occlusions. No distant metastases were found grossly, but in microscopical sections of the lung a very large proportion of the minute pulmonary arteries were solidly plugged with tumor thrombi, and quite probably in the terminal days or few weeks of life there was pulmonary hypertension and an element of cor pulmonale.

DR. EDWARD B. BENEDICT: How common are tumor thrombi with hepatoma?

DR. MALLORY: Four cases out of 5 invade the intrahepatic veins, usually the hepatic, sometimes the portal radicles. It is an exceptional case in which the tumor thrombus occludes the vena cava and grows into the right auricle, but we have seen it on several occasions. The one other tumor in which invasion of veins is equally extensive is hypernephroma, which can also grow up the vena cava and directly in the auricle.

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OCTOBER MEETING OF THE COUNCIL

THE fall meeting of the Council of the Massachusetts Medical Society was held on October 5 with President Arthur W. Allen in the chair. Owing in some part at least to a careful screening of the Society's business by the Executive Committee, the Council nearly broke a record for neatness and dispatch in the performance of its functions.

The deaths of two councilors, Dr. Harold G. Giddings, of Middlesex South, and Dr. Henry A. Robinson, of Norfolk South, was announced, and solemn tribute was paid to their memories.

Various matters of interest and importance were considered by the Council and disposed of according to their merits. Important among these was the approval of the creation of a new representative committee, composed of the secretaries of the district societies, to study the question of redistricting the Society and changing the ratio of representation in the Council.

Dr. Elmer S. Bagnall, of Essex North, a former president of the Society, held in warm regard and widely recognized for the intelligent devotion with which he has served his profession and his community, was unanimously acclaimed as the Society's candidate for the General Practitioner's Award of the American Medical Association.

On recommendation of the Committee on Public Relations, the Council voted to establish a Massachusetts Medical Society citation to be awarded to a layman or a group of laymen for outstanding contributions to medical progress. No more than three such awards are to be made in any one year. It was proposed that this award be named in honor of Lemuel Shattuck, onetime bookseller of Boston and perhaps the country's most distinguished lay contributor to progress in public health. This opportunity was rejected.

The proposal of the Committee on Membership that the by-laws be changed to permit a graduate of a foreign or unapproved school to become eligible for membership in the Society after he "has possessed a license to practice medicine in the Commonwealth and has conducted that practice in the district from which he makes application, for at least one year," was unanimously approved.

The recommendation of the Committee on Society Headquarters that a professional survey be made of the domiciliary needs of the Society, the Medical Library and the *Journal* was approved. A new publicity code designed to help in guiding the public utterances of fellows of the Society was adopted.

MASTERS OF INDUSTRIAL HEALTH

SIR WILLIAM OSLER, whose life can now be viewed with the added respect that a generation of progress has lent, saw with clarity that the advances chronicled in the successive editions of his great textbook were not final achievements but rather steps toward an ever-expanding medical horizon and a new type of practice — preventive medicine. It is doubtful whether he could foresee in detail the development of this kind of Chinese medicine in which the physician is paid to keep his patient well, but he had faith in its possibilities and prophesied that "preventive medicine is the medicine of the future."

Shortly after Osler's death, Harvard School of Public Health appeared as an offshoot of the Harvard Medical School. The institution prospered and came to maturity two years ago with a faculty all its own. Recently, its curriculum committee has prepared an analysis of the objectives and content of public health, wherein is surveyed anew the highway that Osler glimpsed as a freshly blazed trail. Taking into account contemporary knowledge of the theory and practice of physic, the report defines the three basic disciplines essential to a knowledge of public health as ecology, the science of the relations of organisms to each other; epidemiology, the science of the origins and distributions of disease; and biostatistics, the calculus of probabilities by which quantitation is brought to both.

With these studies as a background, the future student of public health can choose appropriate electives depending on whether his chosen career is in such fields as public-health practice, nutrition, tropical medicine and maternal and child health. The analogy with conventional medical training is now complete. Each kind of school stipulates required courses in its basic sciences and offers further electives for the specialist.

Along with the new course in ecology given for the first time this fall, the Harvard School of Public Health will confer the newly established degree of master of industrial health. Besides the sciences already listed, courses for the candidates will cover basic problems in industrial hygiene and organization, and include environmental physiology, sanitation and the control of industrial air hazards.

Something that cannot be taught in courses is also offered to the future graduate when he departs with his degree. This is the opportunity to contribute significantly to the advance of medicine. Most of the great industries have group insurance plans, and the mortality and morbidity data hidden in such files may well be the source of vital statistics pointing to the causes of some of the most serious and crippling diseases. Assuredly, these masters of industrial health will find divisions of their industries in which accidents are a problem, where causes can be determined and effective control measures introduced.[1] Perhaps they will find pulmonary cancers a problem like that among chromate workers.[2] But what about arthritis, peptic ulcer, coronary thrombosis, hypertension and vascular and mental diseases whose causes are at present largely unknown? It may well be that in particular departments of an industry death rates and morbidity rates for some one or other of such diseases — arthritis, for example — may be so excessive as to be significant of the factors acting to produce it. There is the opportunity for the "master" of industrial hygiene to contribute to the ever-growing knowledge of epidemiology and ecology and preventive medicine.

The biochemist has recently developed compound E as a brilliant contribution to the treatment of arthritis. It remains for some future scientist, chemist, clinician or specialist, perhaps with a degree of master of industrial health after his name, to elucidate its pathogenesis. The quest continues for causes. The industrial physician — and the practicing physician — will do well to interpret Osler's kind of observations, whether they are made in the plant, at the bedside or in the laboratory, with Karl Meyer's[3] kind of philosophy when he set his sights on the main road block preventing the advance of preventive medicine:

> Just as in medicine, the foundation of preventive veterinary [or industrial] medicine is a broad knowledge of the nature of disease. The concept of the contagious nature of disease inspired magnificent advances . . . . The reduction in the number of deaths due to infectious diseases attests to its value. But today, the doctrine that there is a single specific cause for each disease entity is untenable. A purely bacteriologic [or chemical] explanation pays little heed to the fact that the essentials of disease are two — an animal and an organism [or a physical or chemical agent]; these interact, react, and are acted upon by external forces. The more quickly it is recognized that causation is a constellation of predisposing, provoking, and perpetuating factors, the more certain will progress be made. To reduce the approach to every disease to concern with one provoking factor continues to retard progress.

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INNER CONFLICT

The series of articles on disabilities, published at intervals by *The Lancet* and once commented on editorially in the *Journal*,[1] has continued for over a year to present its stimulating messages.

Written by the disabled persons themselves, they are usually from the pens of laymen. The story of forty-five years of compromise with a duodenal ulcer, however, is by a physician.[2]

This doctor, leading "a strenuous professional life that has yielded at least a modicum of success and perhaps even a little distinction," experienced his first attack of acute pain at the age of eighteen. From that time on his existence, far too familiar to many persons, was the usual one of repeated episodes of discomfort and pain, and of the conquest of discouragement.

This victim learned that the details of diet, alcohol, tobacco and exercise are personal ones; that the treatment must be the one best adapted to the needs and the temperament of the individual patient. He learned, as have many others, that bed is more valuable than diet; that rest and relaxation and an unfretted mind are more soothing than powders or drops of belladonna.

Ulcer, the "wound stripe of civilization," the torment of the ambitious and the penalty that the conscientious must too often pay, has become synonymous with the gnawing pain that robs one of his rest and removes the joy from living. Every ulcer casualty is the Spartan youth who kept the fox hidden beneath his cloak, even while it devoured his vitals. Nearly thirty-five years ago, intrepid Serbia, which would not let the captive Balkans sleep, became known as the "Serbian ulcer."

In general, as is known only too well in this country, "the sufferer from duodenal ulcer is characteristically of the type that will not compromise. . . . Unless some catastrophe such as haemorrhage or perforation makes surrender incontestable, he will persist in the thick of the fight, even with one hand tied behind his back."

When his ulcer is not troubling him he cannot remember it; when its symptoms recur it will not let him forget its presence. Infrequently fatal, rarely completely incapacitating, the ubiquitous, unpredictable ulcer can hardly be classed among the dramatic calamities from which man's life and health may suffer. "And yet, . . .it may be said that one's enjoyment of life is reduced by an ulcer to a greater extent than by some of the more serious disabilities" — except perhaps for those persons who, regardless of their type, are able and willing to spend their lives in that compromise so distant from their natures.

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YOUNG MAN, GO WEST

Even free enterprise can learn a thing or two when it follows Horace Greeley's injunction to the Young Man. California Physicians' Service,— a Blue Shield Plan,— eager to help the visitor to California's shores, has inaugurated a courtesy travel service available to any of the physicians or lay people connected with any plan that is a member of the Associated Medical Care Plans.

In obtaining hotel rooms or travel reservations, giving advice on the best fishing grounds or tourist resorts, providing forwarding addresses, and even furnishing stenographic assistance, the two main offices as well as the fifteen district offices are at the visitor's service. This year and next are California's centennial years, during which a new pilgrimage of forty-niners is striking west. Members of Associated Medical Care Plans who are directing their steps toward the setting sun should jot the two addresses of Travel Department, California Physicians' Service, on their cuffs: 450 Mission Street, San Francisco 5, and 431 South Fairfax, Los Angeles 45.

Dr. Martin, of Hinsdale, N. H., was fined $75 for violation of the liquor law in that State, by the Court of Common Pleas and yet he only sold it as a medicine, being himself a temperance man.

Boston M. & S. J., *October 17, 1849*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

BACTERIOLOGIC SPECIMENS DELAYED IN THE MAIL

Physicians are advised that diagnostic specimens are not infrequently delayed in the mail, particularly if mailed near the end of the week. When important treatment is dependent upon an early report, it is wise, at least in the metropolitan area, where the distance is not too great, to send the specimen directly to the laboratory by special messenger.

Physicians are reminded that the diagnosis of diphtheria is a clinical and not a laboratory responsibility. Delay in the administration of antitoxin pending laboratory confirmation is very dangerous, and may result in a fatal outcome for the patient. Furthermore, a negative laboratory report does not exclude the diagnosis of clinical diphtheria, for the throat swab may not have reached the actual focus of the diphtheria organism. Since treatment for diphtheria may render a culture negative that would otherwise be positive, specimens should always be taken *before* treatment is begun.

MISCELLANY

STUART McGUIRE LECTURE SERIES AND SYMPOSIUM ON HEMATOLOGY

The twenty-first annual Stuart McGuire Lecture Series and Symposium on Hematology were held at the Medical College of Virginia in Richmond from September 28 to October 1. Sir Lionel E. H. Whitby, Regius Professor of Physic, Department of Medicine, Cambridge, England, delivered the lectures, entitled "The Physiology of Hemopoiesis," "Dyshemopoiesis from Nutritional and Specific Deficiencies" and "Dyshemopoiesis from Noxious Agents." New England was represented at the symposium by William P. Murphy, M.D., of Boston, who spoke on the subjects "The Treatment of Pernicious Anemia" and "Some Frequently Overlooked Sources of Anemia"; Louis K. Diamond, M.D., of Boston, who spoke on the subjects "The Anemias Resulting from Rh Incompatibility" and "Anemias of Childhood"; Thomas H. Ham, M.D., of Boston, who spoke on the subject "Acquired Hemolytic Anemia"; and F. H. L. Taylor, of Boston, who spoke on the subject "Recent Advances in Hemophilia."

NEW DIRECTOR OF RING SANATORIUM AND HOSPITAL

Dr. Benjamin Simon was recently appointed medical director of the Ring Sanatorium and Hospital in Arlington Heights, Massachusetts, succeeding Dr. Charles E. White. Dr. Simon, who received his degree from Washington University School of Medicine, was formerly assistant clinical professor of psychiatry and mental hygiene at Yale University School of Medicine and attending psychiatrist at the Veterans Administration Hospital in Newington, Connecticut, as well as acting assistant superintendent at Worcester State Hospital and clinical director of the Connecticut State Hospital. He is chairman of the New England Regional Survey Committee of the American Academy of Neurology.

BOOK REVIEW

Æsculapius Comes to the Colonies: The story of the early days of medicine in the thirteen original colonies. By Maurice B. Gordon, M.D. 8°, cloth, 560 pp., with 107 illustrations. Ventnor, New Jersey: Ventnor Publishers, Incorporated, 1949. $10.00.

This history of early Colonial medicine in the United States is arranged by states, according to their dates of founding, beginning with Virginia and ending with Georgia, the last British colony to be founded. The work is a compilation from acknowledged sources, which are listed by states in the final chapter. It is noted that certain important sources relating to medicine in Massachusetts have been omitted.

The material in Dr. Gordon's history is well arranged. There is a very good index. The publishing is excellent. A soft, light, nonglare paper is used, making the volume easy to handle. The illustrations on plate paper are tipped into the text. The volume should be in all medical and public libraries.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Blood Transfusion. By Elmer L. DeGowin, M.D., associate professor of internal medicine, State University of Iowa, College of Medicine, director, Blood Transfusion Service, University Hospitals, member of the Committee on Blood and Blood Derivatives, National Research Council, and member of the Advisory Board for Health Services, American National Red Cross; Robert C. Hardin, M.D., assistant professor of internal medicine, State University of Iowa, College of Medicine; and John B. Alsever, M.D., senior surgeon, United States Public Health Service, and chief, professional standards, Hospital Division, United States Public Health Service. 8°, cloth, 587 pp., with 200 illustrations. Philadelphia: W. B. Saunders Company, 1949. $9.00.

In this new book the authors cover the entire field of blood transfusion, including whole blood, to which they have given over one hundred pages. The authors, internists, with an experience individually of ten years in the subject, believe "that whole blood transfusion is still, and will continue to be the major need in the treatment of patients." The early chapters are devoted to a short history, the clinical use of blood and its derivatives, immunology of blood and laboratory procedures. The remaining chapters discuss in detail the transfusion of whole blood; preparation and administration of plasma, and of the blood derivatives and plasma substitutes; and transfusion services and apparatus. Lists of references are appended to the various subdivisions of the text. There is a good index. The type and printing are excellent. The book should be in all medical libraries and in the collections of all surgeons.

Searchlights on Delinquency: New psychoanalytic studies. Dedicated to Professor August Aichborn, on the occasion of his seventieth birthday, July 27, 1948. Managing editor: K. R. Eissler, M.D., Ph.D.; chairman of the editorial board, Paul Federn, M.D. 8°, cloth, 456 pp. New York: International Universities Press, Incorporated, 1949. $10.00.

This memorial volume contains contributions by thirty-five authors, covering the whole field of juvenile delinquency. There is a short preface by Ernest Jones, a short biographic sketch of Professor Aichborn, who was a friend and associate of Sigmund Freud and the author of *Wayward Youth*, and a bibliography of his writings. The work is divided into seven parts: general problems; clinical problems; technic and therapy; etiology and development; social psychology; penology; and surveys. There is a paper by Anna Freud entitled "Certain Types and Stages of Social Maladjustment." The book is well published, but the lack of an index mars its excellency. The volume should be in all collections on psychoanalysis and delinquency.

Studi e ricerche sulla manna e mannite naturale. By Domenico Gigante. 8°, paper, 144 pp. Rome: Istituto Poligrafico Dello Stato Libreria, 1948.

This monograph comprises a study of manna, the exudation of the manna ash tree or *Fraxinus ornus*, and mannite or mannitol, its principal constituent, a mild aperient and cholagogue. The study is thorough, considering the pharmacognosy of manna and its chemistry, the dosage of mannite, its method of extraction and preparation and its pharmacology, the action of manna and mannite on gastric function and on intestinal motility, on the liver and biliary tract, and their purgative and diuretic action; their therapeutic use in diseases of the respiratory organs and diabetes; and the use of mannite in functional and radiologic exploration of the biliary tract. Two appendixes consist of receipts for the medical use of manna and mannite and for the dietetic use of mannite in diabetes. A bibliography concludes the text.

Psychodynamics and the Allergic Patient. By Harold A. Abramson, M.D., associate physician for allergy, The Mount Sinai Hospital, New York City, consulting physician for allergy, Sea View Hospital, Staten Island, New York, and assistant professor of physiology, Columbia University College of Physicians and Surgeons. 12°, cloth, 81 pp., with 7 illustrations. Saint Paul: Bruce Publishing Company, 1948. $2.50. (An official publication of the American College of Allergists.)

This special small volume comprises two short essays by Dr. Abramson entitled "Psychomatic Aspects of Hay Fever and Asthma Prior to 1900" and "Psychodynamics and the Allergic Patient," constituting in all thirty-six pages. Appended to the essays is the report of a panel discussion by ten well known authorities on allergy, comprising forty-five pages of text.

Atlas of Oral and Facial Lesions and Color Film Library. By Ralph H. Brodsky, D.M.D., consulting oral surgeon, Department of Hospitals, New York City, lecturer in stomatology, New York University College of Medicine, associate dentist to the Mt. Sinai Hospital, New York, and founder and executive-secretary, Pan American Odontological Association. 8°, cloth, 127 pp., with 100 illustrations. Baltimore: Williams and Wilkins Company, 1948. $80.00.

This atlas, with its accompanying collection of one hundred colored slides, presents a new type of teaching unit for the dentist and oral surgeon. The slides depict lesions of the face and oral cavity. The text, supplied with the film slides, discusses the important features of the lesion, its diagnosis and treatment. Each slide is represented in the text by a diaphragmatic drawing. The slides are contained in a plastic case, bound to match the volume and designed to stand on a shelf with the book.

The Doctor Wears Three Faces. By Mary Bard. 8°, cloth, 254 pp. Philadelphia: J. B. Lippincott Company, 1949. $3.00.

This novel relates the experiences of a doctor's wife, covering all the phases of medical practice and ending with a trip to an American Medical Association convention. The story is well written and entertaining and represents the better type of medical fiction.

Introduction to Physiological and Pathological Chemistry: With laboratory experiments. By L. Earle Arnow, Ph.G., Ph.D., M.B., M.D., director of research, Medical Research Division, Sharp and Dohme, Incorporated, Glenolden, Pennsylvania. With an introduction by Katharine J. Densford, R.N., B.A., M.A., D.Sc., professor of nursing and director of the school of nursing, University of Minnesota, Minneapolis. Third edition. 8°, cloth, 595 pp., with 144 illustrations. St. Louis: C. V. Mosby Company, 1949. $4.00.

This textbook was first published in 1939. The second edition was reprinted four times during 1943–1945, speaking well for the popularity of the book. It is written in a simple manner for students. The text is divided into three parts: introduction to chemical science; physiologic and pathological chemistry; and introduction to laboratory chemistry. An appendix includes tables of the international atomic weights (1947) and chemical components of human blood, and a long article of thirty-five pages on stain removal from fabrics, with home methods, reprinted from *Farmers' Bulletins*, No. 1474. There is a good index. The material is well arranged, and the book well printed. It should prove useful as a ready reference source for medical libraries.

Operative Surgery. By Frederick C. Hill, M.S. (Surg.), M.D., associate professor of surgery, The Creighton University School of Medicine, Omaha, Nebraska. With a foreword by Charles W. Mayo, M.S. (Surg.), M.D., Section on Surgery, Mayo Clinic, Rochester, Minnesota. 8°, cloth, 698 pp., with 255 illustrations. New York: Oxford University Press, 1949. $12.75. (*Oxford Medical Publications.*)

The author presents a treatise of practically pure operative surgery with the objective of providing a single-volume work on general surgery, in which the gross appearance of surgical lesions is described, the proper treatment indicated and detailed description of operative procedures given. There are short chapters on preoperative and postoperative treatment. The classification used is the age-old type of head to foot. The author suggests operations he considers most [illegible] able for the various surgical conditions described. The [illegible] terial is well arranged, and the text well written. The [illegible] is a personal one based on the author's experience and is [illegible] overloaded with redundant references to the surgical literat[illegible] It should prove interesting to all surgeons.

An Introduction to Cardiology. By Geoffrey Bourne, M.[illegible] F.R.C.P., physician, and physician in charge of the Car[illegible] logical Department, St. Bartholomew's Hospital. 8°, cl[illegible] 264 pp., with 65 illustrations. Baltimore: Williams a[illegible] Wilkins Company, 1949. $4.50.

This small manual, which endeavors to portray the cl[illegible] aspects of cardiovascular disease, is based largely on lect[illegible] given at St. Bartholomew's Hospital, London, and on [illegible] author's personal experience. The material is well arrang[illegible] condensed and written. This is a personal book, and referen[illegible] to the literature are omitted from the text. In the introduct[illegible] the author refers to three standard works that he recomme[illegible] for collateral reading, among which he mentions *Heart Dis[illegible]* by Dr. Paul D. White, of Boston, as being the best detai[illegible] textbook on the subject. The book is well published. T[illegible] printing was done in Great Britain.

Thank God for My Heart Attack. By Charles Y. Harri[illegible] 12°, cloth, 144 pp. New York: Henry Holt and Compa[illegible] 1949. $2.50.

This popular book, although it may be classed as n[illegible] fiction, has all the aspects of a novel. Mr. Harrison, a w[illegible] known writer, suffered an attack of coronary thrombo[illegible] from which he recovered. In this book he relates his exp[illegible] ences while he was ill and until the time he returned to [illegible] work of writing. The text is well written and interesti[illegible]

NOTICES

ANNOUNCEMENTS

Dr. Joseph Bernard Doyle announces the removal of h[illegible] office for the practice of gynecology and obstetrics to [illegible] Bay State Road, Boston.

Dr. John J. Finn, Jr., announces the opening of an off[illegible] at 270 Commonwealth Avenue, Boston, for the practice [illegible] internal medicine.

Dr. Milton H. Rodofsky announces the removal of h[illegible] office to 478 Beacon Street, Boston.

Dr. Arthur A. Wills, Jr., has resigned his position as a[illegible] sistant medical director with the Travelers Insurance Co[illegible] pany, Hartford, Connecticut, and plans to resume the pra[illegible] tice of medicine at 815 Sheraton Building, 10 Post Offi[illegible] Square, Boston.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of The New England Society of Anes[illegible] thesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, November 8, at 8:00 p.m. The subject "Decamethonium Iodide: Its Uses in Conjunction with Pentothal Sodium and Nitrous Oxide Oxygen in Abdominal Surgery" by Drs. Francis F. Foldes and Theodore S. Machaj, of the Department of Anesthesia, Mercy Hospital, Pittsburgh, Pennsylvania, will be presented by Dr. Francis F. Foldes.

AMERICAN INSTITUTE OF ARCHITECTS

The six New England chapters of the American Institute of Architects will hold a seminar on hospital design at the Hotel Kenmore, Boston, on December 1 and 2. Leaders in the hospital field will discuss the solution of problems encountered in the design of hospitals of small and medium size. The program will include topics of interest to hospital consultants and administrators and medical personnel, as well as professional architects.

(*Notices concluded on page xv*)